A PROSPECTIVE STUDY ON COMPARISON OF URINARY CYTOLOGY WITH HISTOPATHOLOGICAL EXAMINATION IN BLADDER TRANSITIONAL CELL CARCINOMA

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CERTIFICATE

This is to certify that this dissertation entitled **"A PROSPECTIVE STUDY ON COMPARISON OF URINARY CYTOLOGY WITH HISTOPATHOLOGICAL EXAMINATION IN BLADDER TRANSITIONAL CELL CARCINOMA"** submitted by **Dr. P.VIJAYAKUMAR** appearing for **M.Ch (Urology)** degree examination in August 2015 is a original bonafide record of work done by him during the academic period of August 2012 to July 2015 under direct supervision and guidance in partial fulfillment of requirement of the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION BY THE CANDIDATE

I, **Dr. P.Vijayakumar ,** solemnly declare that this dissertation titled **"A PROSPECTIVE STUDY ON COMPARISON OF URINARY CYTOLOGY WITH HISTOPATHOLOGICAL EXAMINATION IN BLADDER TRANSITIONAL CELL CARCINOMA"** was done by me in the Department of Urology, Kilpauk Medical College Hospital and Government Royapettah Hospital Chennai under the guidance and supervision of **Prof Dr.N.MUTHULATHA, M.S., M.Ch.,** Professor of Urology, Kilpauk Medical College.

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INTRODUCTION

INTRODUCTION

Bladder cancer accounts for 7% of all cancers in male and 2% of all cancers in female. Urinary cytology has prominent role in the multidisciplinary diagnostic approach to bladder cancer. It is used as a valuable adjunct to cystoscopy and biopsy for diagnosis and follow up of patients with bladder cancer

Urine cytology remains gold standard for bladder cancer screening. It is the test against which all others are compared when evaluating potential bladder tumor markers. It has excellent specificity with few false positive cases

Cytological examination of voided urine is a non-invasive screening test for bladder tumors, which can be carried out in remote areas of the country. By cytology one can even classify type and grade malignancy.

In 1945 Papaniculoau and Marshall recommended cytological examination of urinary sediment for diagnosis and follow up of patients with urological malignancies. The prognostic value of conventional cytology to monitor patients with superficial bladder carcinoma is well established. While cystoscopy and biopsy are optimum for diagnosis of visible disease, entire bladder mucosa can be sampled by cytology, enabling detection of occult urothelial abnormalities.

Traditionally cytological examinations have been used to detect in situ and early invasive bladder cancer in high-risk population and in conjunction with

cystoscopy and biopsy to diagnose new or recurrent bladder tumor. Cytology also has been used to identify persistent tumor after transurethral resection.

Urine Cytological examination is a simple, safe, and inexpensive method to detect hidden urothelial tumours. Urinary tract tumours are often multifocal. Indications for urine cytology examinations are 1) detection and diagnosis of tumours, carcinoma in situ, inaccessible lesions in ureters, pelvis, diverticuli, 2) Screening of high risk patients

(chemical or metal exposure, smokers) 3) Monitor tumours and therapy

Cystoscopy remains the standard for the diagnosis and surveillance of bladder tumors, allowing the lesions to be mapped and sampled. However, cystoscopy cannot explore whole bladder urothelium, and cannot diagnose all carcinoma in situ cases or lesions of upper urinary tract. Thus, it must be combined with urinary cytology, particularly in search for tumor cells from high-grade lesions, wherever their location in the urinary tract.

Urine cytology can detect bladder tumor before it can be detected cystoscopically. Urine cytology is still indispensable in the management of patients with transitional cell carcinoma. It remains as a gold standard for bladder cancer screening. All Ultrasound detected bladder neoplasm will be screened by urine cytology collected randomly. Urine cytology will be corroborated with histopathological examinations

AIM OF THE STUDY

AIMS OF THE STUDY

1. To Correlate Urine cytology with Histopathology of the Bladder Transitional Cell Carcinoma.

2. To Study the Role of Urinary Cytology in the diagnosis of Bladder Transitional Cell Carcinoma.

3. To Find out the Correlation between the Grading by Urine cytology and Histopathology.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Bladder cancer is three times more common in male than female and twice as common among whites compared to blacks. Bladder cancer was first noted in man worked in aniline dye industry in 1895. Common age group is 65 to 70 years old. Most of patients are older than 50 years of age

The bladder stores temporarily concentrated toxic products of renal excretion and is exposure to environmental carcinogens. Aniline dyes containing arylamines, e.g.benzidine, beta naphthylamine are most important risk factors for the development of transitional cell carcinoma. High-risk occupations include chemical, dye, textile, rubber, and plastic workers as well as painters and hairdressers. Cigarette smoking is one of risk factor for bladder cancer. Certain drugs [eg.chemotherapeutic agents, phenacetin and opiates] are highly associated with the development of bladder cancer.

Schistosoma haematobium infection is a risk factor for sqamous cell carcinoma. Previous Radiation exposure of the bladder increases the risk of urothelial carcinoma. Certain genetic alterations are observed in urothelial cell carcinoma, comman are chromosome 9 monosomy or deletions of 9p and 9q, deletions of 17p, 13q, 11p and 14q.

The Genetic pathway, which is initiated by deletions of tumor suppressor genes on 9p and 9q leads to superficial papillary tumors, a few of which may then acquire P53 mutations and progress to muscle invasion.

Initiation by P53 mutation, second pathway, which leads to carcinoma in situ and with loss of chromosome 9, progresses to invasion.

The urocarcinogens, by injuring the coding units of the urothelial cells, render them defective, leading to hyperplasia and neoplasia, with the action of promoters.

TUMORS OF THE URINARY BLADDER[17]

Benign epithelial tumors

Typical papilloma

Inverted papilloma

Villous adenoma

Mucinous cystadenoma of the urachus

Squamous papilloma

Malignant epithelial tumors

Transitional cell carcinoma

Papillary

(1) Superficial

(2) Muscle - invasive

Non-papillary

(1) Transitional cell carcinoma in-situ

(2) Invasive transitional cell carcinoma

Squamous cell carcinoma.

Adenocarcinoma

Carcinomas of more than one histologic type

Mesenchymal tumors

Benign

Malignant

(1) Leiomyosarcoma

(2) Rhabdomyosarcoma

(3) Others

Mixed tumors

Adenofibromas and adenosarcomas

Carcinosarcoma

Hematopoietic neoplasms

Lymphoma

Leukemia

Plasmacytoma

Miscellaneous primary tumors

Paraganglioma

Carcinoid

Malignant melanoma

Dermoid cyst

Yolk sac tumor .

Metastatic tumors

URINE CYTOLOGY

Tumor cells in the urine were noticed first by Sanders in 1864 and Dickson in 1869. In 1892, Ferguson suggested that microscopic examination of the urine sediment, except for cystoscopy was the best method for diagnosing tumors of the bladder. In 1895, Rovising reported malignant cells in the urine sediment of 3 out of 7 patients with kidney tumors.

In 1928, Zemansky correlated urinary findings with subsequent tissue examination in 46 cases of suspected tumors and reported urine unfit for cytologic study. Cytologic diagnosis Interest is waned until the studies by Papanicolaou and Marshell in 1945, supplemented by Papanicolaou a year later, he demonstrated the usefulness of smear technique in diagnosing cancers of urinary organs. They considered urine sediment most suitable for the identification of cells with malignant characteristics, Because of the normal desquamation from epithelial surfaces, which increases in the presence of neoplasia[32].

In 1945, Papanicolaou and Marshall demonstrated that a bladder tumor undergoes exfoliation, which renders possible its recognition by detection of abnormal cells in the urine, cytology has become an important adjuvant for the diagnosis and follow up of patients with cancer. Umiker et al, In 1964 reviewed the literature on the role of urinary cytology and found positive results ranging from 26.1 to 100% with an average of 71.6%. In 1972, Harris and associates performed bladder irrigation, his yield improved by 30% over urinary cytology.

In 1970, Esposti and associates recognised the importance of the pathological grading of the tumour in influencing the cytological results[43].

Tumours of the urinary tract are relatively inaccessible to direct biopsy and the tumours are often multifocal. Since the entire mucosal surface is bathed in urine, in theory urine is the perfect specimen to examine for evidence of tumor in the urinary tract.

Urinary cytology is useful in the detection of

1. Carcinoma in situ.
2. Urothelial carcinoma in its preclinical phase
3. Follow up of patients after treatment to detect any residual or recurrent tumours.

Cytologic examination of the sediment of voided urine is the noninvasive method of detection, diagnosis and follow up of tumours of the bladder, upper tract and other anatomic components of the lower urinary tract. Urine cytology is a cost effective method.

Urine cytology remains gold standard for bladder cancer screening. Urine cytology is the test against which all others are compared when evaluating potential bladder tumor markers. It has excellent specificity with few false positive cases. High grade malignant cells are detected by urine cytology, even before a cystoscopically distinguishable gross lesion. It’s

capable of detecting malignant non-exophytic tumour types than that ultrasound cannot detect[34].

In 1980, study conducted by M. N. EL-Bolkainy showed that the cytology is highly effective in the primary diagnosis of high grade transitional cell carcinoma with a positive rate of 93-94.7%.

The study conducted by Leopold G. Koss et al 1985 also showed that for diagnosis of high grade tumours, cytology of voided urine is highly reliable in the with a sensitivity of 94.2%. The sensitivity was about 100% in primary flat carcinoma in situ

In Patients with low-grade non-invasive tumours can be followed up cytologically. Patients with high-grade cytological abnormalities predict an aggressive tumour course , increase risk of recurrence, while negative cytological findings have a very low risk of recurrence.

The study conducted by Niels Harving et al 1988 , concluded that urinary cytology is also better indicator of the presence of concomitant urothelial atypia than preselected mucosal biopsies.

Post operative (radical operation) examination of urine cytology for malignant cells should be monitored for development of new tumors in the kidney ureter or occasionally in the intestine itself.

Clinical history is important & imperative for the elimination of misdiagnosis. Pertinent information includes the method of specimen collection,

the presence of calculi and past therapies. To use urine cytology most effectively it is important first to understand its advantages and limitations.

Advantages of voided urine cytology.

1. Simple, can be easily collected.
2. Repeated if necessary, with little or no inconvenience for the patient.
3. Inexpensive.
4. Non invasive.
5. Can be done even in remote areas of the country.
6. Detects high grade malignancy before cystoscopy can detect.
7. Samples of urine may contain representative cells from the entire urinary tract. So that the entire system can be surveyed.

Disadvantages of voided urine cytology

1. Low cellularity.
2. Contamination from female genital tract.
3. Not localizes the tumor
4. May contain degenerated cells or reactive transitional cells which may give false positive results.

An important diagnostic principle is that higher the grade of the tumor, the more accurate the diagnosis. For diagnostic inaccuracy, there are several reasons. Urine is an inhospitable environment for cells. So degenerative changes that make diagnosis difficult are common.

False positive results can occur due to misreading of atypical cellular changes as malignant. Common causes of cellular atypia are cystitis, senile prostate, calculi, chemotherapy and radiotherapy effects, and virus infection.

Positive urine cytologic diagnosis should always be confirmed histologically, before definitive therapy is instituted, because False positive diagnosis of bladder cancer may lead to radical therapy[37]. Most patients with false positive cytological findings may develop a tumor in subsequent years and therefore need repeated examinations of urine for malignant cells

False negative diagnosis may be of more important clinical consequence. In diagnosis of papilloma and well differentiated transitional cell carcinoma, cytology can be difficult or impossible because the cells are nearly normal appearing. False negative diagnosis mainly due to low cellularity, poor preservation or obscuring of malignant cells by inflammatory cells.

Suboptimal Specimen

According to Sheldon Bastacky et a[41] 1999, suboptimal urinary specimen is considered, if the specimen had one or more of the following deficiencies

1. Less than 15 intermediate or basal urothelial cells.
2. Obscuring of malignant cells by red blood cells or inflammatory cells.
3. Poor cellular preservation.

Following newer diagnostic techniques have been studied to increase diagnostic efficacy.

- Flow cytometry[39].
- Image analysis.
- Assay of Nuclear matrix protein 22 (NMP22)[40]
- Immune histochemical analysis of p53 over expression[21].
- Immunology e.g.-blood group isoantigens and monoclonal antibodies to a variety of tumor associated antigens[40].
- Telomerase activity[40]
- Aura Tek FDP assay (Fibrin/Fibrinogen Degradation products).
- Detecting hyaluronic acid/ Hyaluronidase levels[11].

BASIC SPECIMEN

There are three basic types of exfoliated urinary tract specimens:

(1) Voided urine

(2) Catheterized urine, and

(3) Brushing/washing specimens

"Clean catch" voided urine is recommended for screening purposes. However, in some cases bladder washing may be the method of choice in which there is a high clinical suspicion for bladder malignancy.

Specimens should be processed immediately or refrigerated and processed as soon as possible. Immediate fixation with 50% ethanol may preserve the specimen for several days, If a delay is anticipated[30,51].

A solution of 25% ethanol [equal volume of 50% ethanol and urine.] is widely used. This recommended percentage is in order to lessen the shrinkage and hardening effects of more concentrated solution[52].

All urine cytology specimens are dilute sufficiently as to require some form of cell concentration. Initially, cytologic findings were assesed on smears made from the sediment of centrifuged specimen. Subsequently developed methods include thin membrane filtration, cytocentrifugation and most recently mono layer technique[11].

Urinary samples can be processed by the several techniques including direct smears, membrane filters and cytocentrifugation. Every techniques has certain advantages and disadvantages. In general direct smears are easiest to prepare, but suffer from suboptimal display of cellular details and high cell loss. Membrane filters techniques produce the best cytologic details, but are difficult to prepare[51].

Cytocentrifugation and Cytyc thinprep liquid based cytology are appropriate methods for cytology based molecular studies but cytocentrifugation is the quality standard for current treatment of urinary samples because of its lower cost[9].

Papanicolaou stain is most usually preferred. Since fine nuclear detail is often crucial to proper diagnosis.

Voided Urine

Normal voided urine usually contains only a few cells. Normal urine contains approximately 10 cells/ml[51]. Voided urine also contains significant amount of vaginal and skin contamination particularly in female. Increased cellularity may be seen with instrumentation, stones or neoplasms.

The transitional cells in urine usually have a trapezoidal (truncated pyramid or trapezium) shape. The transitional cells in a voided urine specimen are relatively uniform. However, cells can be vary from parabasal to relatively large. The nuclei are vary from round to oval with smooth nuclear membranes. The chromatin is either delicate or condensed. Small nucleoli may be seen. There is usually contain a moderate amount of cytoplasm[37].

Urine cytology should be performed on freshly voided urine . The most useful sample is mid morning sample. Fractionated cytology usually did not improve the diagnostic accuracy of urinary cytology and that any part of voided stream is adequate for cytological purposes[22]. Samples must be collected in a clean container and immediately sent to the laboratory. If the specimen has to be transported or kept overnight to preserve the cells alcohol should be added

By using adhesive fluids Cell loss from slides can be minimized. The paraffin blocks of sediments are useful in identification of papillary tumor fragments in the specimen.

There must be three optimum number of voided urine samples to submit. Of the neoplasms that can be diagnosed with voided urine cytology, about 80% will be on the first specimen, 15% on the second, and the rest on the third[34].

Degenerative changes, are common in voided urine specimens. Factors causing degeneration include variable osmolality of the urine and high acidity. Degeneration of urothelial cells begin prior to exfoliation and continuous while the cells are in contact with urine prior to and after voiding.

Specimen should not be submitted from first morning voiding, 24 hours collection or drainage bags because prolonged exposure of urothelial cells to urine causes degenerative changes.

Catheterized urine

Simple catheterization usually increases the cellularity over voided urine specimens, and specimen may be somewhat better preserved. However, it makes the diagnosis of low-grade lesions more difficult because pseudo papillary clusters may be present, and lesions in the urethra may be missed.

Bladder wash

Bladder wash specimens are superiorly diagnostic to voided urine specimens. Has better preservation of specimen, more cellular and there is less contamination of the background than voided urine specimen. It is important

that the urologist submit both the urine present in the bladder and the saline wash at cystoscopy ("cysto urine"). Cysto urine usually does pick up a significant number of additional cases of cancer.

To detect lesions in the urethra, freshly voided urine specimen should be submitted. Although bladder washing is superior to voided urine in diagnosis, it is inconvenient, relatively expensive, uncomfortable, and has a risk of infection.

Advantages and Disadvantages of Voided Urine and Bladder Washing Specimen.

Advantages	**Disadvantages**
Voided urine	
Easy to obtain specimen Good sensitivity for high- grade tumor Sample entire tract	Degeneration Few cells, particularly in lowgrade tumor Contamination, especially from female genital tract
Bladder washing	
Excellent preservation High sensitivity, Almost no contamination	Inconvenient, uncomfortable, expensive Possible risk of infection, spread of tumor Limited sample

UROTHELIAL CELLS

Urothelium is composed of superficial layer of large cells which cover several layers of uniform smaller cells like an umbrella, hence named umbrella cells. Superficial cells have abundant cytoplasm and typical and convex, concave surfaces with multiple nucleoli. They have a rigid surface membrane which does not round up in fluid environment. So that these superficial cell elements are readily identified in urinary samples. It produce and secrete small amount of mucin.

Reactive superficial cell may look like a high grade neoplastic cell but truly malignant cells rarely if ever differentiate towards superficial cells. So these cells should not be misinterpreted as neoplastic cells . when N; C ratio (Nuclear; Cytoplasmic) of 1: 2 or less should be considered malignant.

Sub superficial transitional cells lie beneath the superficial cell layer. They are uniform, smaller, normally filled with glycogen which washes out during processing leaving a cleared cytoplasm, surrounding an ovoid nucleus. These cells are arranged in 3 to 4 cell thick layers but probably not exceeding 6. They are inactive, replicate every 200 to 500 days. In urinary specimen, these cells tend to cluster . Instrumentation can produce papillary aggregates in urine as false positive, but these aggregates are having smooth borders and cells are uniform. Papillary configuration per se is an unreliable feature of neoplasia. Reactive sub superficial transitional cells develop nuclear enlargement, cytoplasmic vacuolation, and prominent nucleoli[51].

Most neoplastic cells tend to be differentiate toward subsuperficial urothelial cells .It is these elements to which comparison of nuclear characteristics between neoplasia and normal are made.

Cytoplasmic vacuolization and prominent nucleoli can be seen in either reactive transitional cells or in high grade transitional cell carcinoma, but their presence excludes low grade transitional cell carcinoma.

Degenerated Transitional Cells

Degeneration caused by inflammation, stones, trauma, etc can result in bizarre transitional cells contain darkly condensed coarse or pyknotic chromatin Although,chromatin of these benign cells is usually smudged or degenerated such changes can resemble cancer. In contrast, the chromatin granules of cancerous cells are characteristically crisp and well preserved. In degenerated transitional cells , Margination of the chromatin, with central clearing, is also frequent. Degenerated nuclei may further undergo karyolysis and karyorrhexis and become washed out or broken up. The cytoplasm may disintegrate and be merely a tag attached to the nucleus (comet cell) or absent together[37]

Significance of Papillary Clusters.

Papillary aggregates produced by Instrumentation, catheterization or even simple manipulation of the bladder, that mimic tissue fragments detached from low grade papillary tumors.

The papillae from transitional cell carcinoma tend to be crowded and disorganized, with irregular borders and mild nuclear atypia, while post instrumentation pseudo-papillae tend to be ball-shaped, cohesive, or papillary clusters with smooth borders outlined by a densely staining cytoplasmic collar. However, when papillary clusters are shed in urine in low grade transitional cell carcinoma, they may be confused with artifacts induced by instrumentation[45].

Uniform central nuclei, smooth nuclear membranes, fine even chromatin, cytoplasmic vacuoles, low N/C ratios and general lack of crowding favor a benign diagnosis[16].

Squamous Cells and Squamous Metaplasia

Squamous cells are also common finding in urine specimens. Source of squamous cells are contamination of urine by squamous cells from urethral meatus, female genital tract, cells from trigone, metaplastic squamous cells.

In chronic inflammation or irritation (stones, indwelling catheter), Squamous metaplasia occurs The metaplastic cells are usually intermediate, mature, or superficial squamous cells. Squamous metaplasia should be diagnosed only after exclusion of contamination, thus usually it requires a catheterized specimen.

Columnar cells

Columnar cells generally account for less than 5% of all cells in a urinary specimen. They commonly appear after prostatic surgery or instrumentation[75].

Red blood cells and inflammatory cells

Normally the urine is usually free of inflammatory cells and RBCs. Significant numbers indicate disease or trauma and when abundant may obscure the presence of tumor cells. Hematuria results from any disease or trauma to the Kidney and/or urinary tract and is seen with calculi, neoplasm, infections

Cellular Reaction to Therapeutic Agents

1. Cyclophosphamide is a alkylating agent given systemically and metabolized to active form. The active form is mostly concentrated in urine and remains in contact with urothelial cells for relatively prolonged periods until voided. Cyclophosphamide causes cellular atypia it closely mimic cancer. The presence of multinucleated cells with signs of nuclear degeneration (karyorrhexis, lysis, and nuclear vacuolization) suggests chemotherapy effect.

2. Alkylated agents like Mitomycin C and Thiotepa are topically applied administrated in their active form for prevention or treatment of bladder neoplasm. The drugs remain in contact with urothelium for limited periods prior to voiding. Their cytologic manifestations are confined almost exclusively to superficial cells, where they cause enlargement of both cytoplasm and nuclei resulting in characteristic but bizarre cells. Nuclei are usually not hyperchromatic but those that are usually have smudgy appearing chromatin. Multiple small nucleoli are common. The cytoplasm is degenerated, vacuolated and frayed.

3. Bacillus Calmette-Guérin [BCG] vaccine is an increasingly common therapeutic agent for bladder cancer that is particularly effective in treating carcinoma in situ. BCG therapy can also cause epithelial atypia, including slight nuclear hyperchromasia with cytoplasmic basophilia. In contrast with cancer, the N/C ratio is preserved and the nuclear membranes are smooth. Significant nuclear pleomorphism, prominent nucleoli, or cytomegaly are not seen in the transitional cells.

Radiation

Radiation can cause certain cytologic changes, especially multinucleation, cytoplasmic vacuolization and nuclear pyknosis. Bizarre nuclear abnormalities can occur[51].

It is not possible to distinguish with any degree of certainity malignant from non-malignant irradiated urothelial cells in urine. History of previous irradiation should be given to the cytologist.If numerous bizarre cells appear long after radiation, or if there has been an interim period when cytologic appearances were normal, then recurrence is strongly suggested[36].

The interpretation of urine cytology were classifieds as

Negative : Normal transtitional cells

Atypia : Atypical cells in loose clusters with slightly increased nuclear cytoplasmic ratio with fine chromatin and small nucleoli

Suspcious: Cells with abnormal features short definite diagnosis of malignancy

Positive: Loose clusters or isolated cells with increased nuclear cytoplasmic ratio with fine to coarse chromatin and prominent nucleoli

For this purpose of study cytological negative, atypical/ reactive and degenerated smears are combined into one group i.e. cytologic negative. Suspicious and positive smears were combined into another group i.e. cytologic positive.

Papanicoloau staining

Staining Technique

1. Fix smears (while still moist) in equal parts of alcohol and ether for 15 - 30 minutes.
2. Rinse smears in distilled water.
3. Stain in Harri's Haematoxylin for 4 mts.
4. Wash in tap water for1-2mts.
5. Differentiate in acid alcohol.
6. Blue in tap water or 1.5%sodium bicarbonate
7. Rinse in distilled water.
8. Transfer to70% then 95% alcohol for few seconds.
9. Stain in OG-6 for 1-2 mts
10. Rinse in 3 changes of 95% alcohol for few seconds each.

11. Stain in EA-36 for 1 - 2 mts

12. Rinse in 3 changes of 95% alcohol for few seconds each

13. Dehydrate in absolute alcohol, clear in xyol and mount in DPX.[Distrene Dibutylphthalate Xlol]

Result

Nuclei - Blue

Acidophilic cells - Red to Orange

Basophilic cells - Green to blue green

Cells or fragments of tissue penetrated by blood- Orange to Orange Green

Criteria for cytological diagnosis

Atypical/reactive cells

Enlarged cells with vacuolated cytoplasm and large centrally placed nuclei with smooth nuclear borders and multiple prominent nucleoli and fine even chromatin were diagnosed as atypical/reactive cells

Degenerated cells

Cells with disintegrated cytoplasm, smudged or degenerated chromatin and degenerated nuclei were diagnosed as degenerated cells.

Suspicious cells

The diagnosis of suspicious was rendered when the evidence was judged to be strongly suggestive of cancer but insufficient for an outright- diagnosis.

H & E staining [Heamatoxylin and Eosin] for tissue sections

Staining technique

1. Dewax sections, hydrate, through graded alcohol to water

2. Remove fixation pigments if necessary.

3. Stain in alum hematoxylin of choice for a suitable time.

4. Wash well in running tap water until sections 'blue' for 5 minutes or less.

5. Differentiate in 1% acid alcohol (1% Hcl in 70% alcohol) for 5- 10 sec

6. Wash well in tap water until sections are again blue (10 - 15 minutes) or

7. Blue by dipping in an alkaline solution (eg ammonia water) followed by a 5 min tap water wash.

8. Stain in 1% eosin for 10 minutes

9. Wash in running tap water for 1 - 5 minutes

10.Dehydrate through alcohols, clear and mount.

Results

Nuclei - blue/black

Cytoplasm - varying shades of pink

Muscle fibres - Deep pink/red

RBC[Red blood Cells] -Orange/red

Fibrin - deep pink

For heamatoxylin and eosin staining of cytology smears 0.5% acid alcohol is used for differentiation

Histopathology slides were diagnosed as

No malignancy

Low grade transitional cell carcinoma

High grade transitional cell carcinoma

Then Cyto - Histological correlation was done.

Correlation was also done with cystoscopic findings and cytological, histopathalogical findings. Histological diagnosis was based on WHO grading. The tumors showing delicate orderly arranged papillary structures with minimal crowding, with enlarged cells, round to oval slightly variable sized nuclei, inconspicuous nucleoli and occasionally found mitosis were classified as low grade transitional cell carcinoma. The tumors showing disorderly arranged papillary structures with loss of polarity, enlarged cells with pleomorphic nuclei showing multiple prominent nucleoli and frequent mitosis were diagnosed as high grade transitional cell carcinoma.

Low-grade transitional cell carcinoma

Papillary or loose clusters of large cells with homogeneous cytoplasm and eccentricity placed enlarged nuclei with irregular nuclear borders, fine even chromatin were diagnosed as low grade transitional cell carcinoma .

High-grade transitional cell carcinoma

Loose clusters or isolated large cells with vacuolated cytoplasm, eccentricity placed pleomeorphic nuclei with increased N/C ratio [Nuclear Cytoplasmic ratio], irregular nuclear borders, coarse uneven chromatin and multiple nucleoli were diagnosed as high grade transitional cell carcinoma.

Cyto-hystological correlation was done patient based rather than specimen based. Such that one patient with multiple specimens, correlation was tabulated only one time.

A positive correlation satisfied one of the two conditions.

1. A patient with at least one positive urinary cytology concurrent with positive histological specimen or
2. A patient with consistently negative urinary cytology and histology specimen.

A discordant correlation was taken when at least one positive diagnosis by either cytology or histology and negative findings by the other modality.

An explanation of discordant results was determined

Urine cytology is a diagnostic tool in detection and follow up of bladder carcinoma. Its reliability has been reduced by relative inexperience of pathologists, by lack of cellular criteria regarding morphology of low grade papillary and flat lesions of bladder. Overall , cytohistologic correlation for patients with bladder cancer was 92%. Positive cytology occur in 63% of patients with grade I transitional cell

carcinoma, suspicious for malignancy in 14%. Dyplastic cells in cytology may represent under interpretation of low grade papillary bladder tumour. The cells of low grade TCC and dyplasia, differ morphologically both from normal and reactive elements, can be detected in cytology specimens. These changes are often subtle and require experience for interpretation.

Urinary cytology was performed on 260 cases of histologically proven urothelial cancer by curling. The size, site, shape and histological grade of tumour was recorded, and classifieds by TNM Staging. Overall, urine cytology was positive in 135, suspicious in 28 and negative in 97 cases. Malignant urothelial tumours were large papillary and solid, moderately or poorly differentiated and invasive T2-4. Most of the upper tract tumours had positive urinary cytology. The study confirms exfoliative urinary cytology is useful in detect malignant bladder tumours including carcinoma in situ and others tumours in less accessible parts of urinary tract.

Another study comparing abdominal ultrasound and cystoscopy was carried out in 187 patients by neils Juul et al. 20 bladder tumours sized from 2 to 5mm were overlooked in cytology. Combination of cytoscopy with urine cytology increased diagnostic sensitivity. To reduce cost effectiveness and patient inconvience in bladder both ultrasound and urine cytology is alternative to cystoscopy, but only in low risk bladder tumour.

O" Donoghue et al (1991), have analysed accuracy of cytological examination in voided urine in a population of 265 patients presented with suspected bladder tumours. Bladder tumours was confirmed by tissue histologically in 51 patients. Of these 42 patients were identified by cytology examination. Overall 34 patients are labelled as malignant on cytology, of which 2 are negative on final histology. 13 patients are labelled as suspicious, but 3 cases are benign on histological diagnosis. These data give sensitivity of urine cytology in diagnosing bladder cancer of 82%, specificity of 97%, positive predictive value of 94% and negative predictive value of 96%.

Ro J Y et al, he compared the cytological and histological features of superficial bladder cancer. Despite technologic advances in diagnostic skills, cytological histological evaluation still standard for the identification of bladder cancer, treatment selection and post treatment survillence. The appropriate collection and handling of sample is the key to proper interpretation of cytological specimens. Depend upon the different histology of tumour, treatment differs. So both urologists and pathologists must known about importance of muscularis mucosa, TCC may invade this layers without extending into true muscle

Ancillary techniques increase the sensitivity of urine cytology have been clinically insignificant. Several bladder tumour markers have been investigated like BTA, nuclear matrix proteins, fibrin degradation products,

have lower specificity than urine cytology and may have increase false positive. Telomerase in highly sensitive and specific, disadvantages as not readily available. Hyaluronidase and hyaluronic acid are important markers, but does not detect grade I TCC. Combination of these tumour markers increases performance status, allow advantages of one another, compared to bladder tumour markers, urine cytology will remain gold standard screening method because of comfortable familiarity.

Cystocopy considered gold standard in diagnosing for recurrent urothelial cell carcinomas. But its both invasive and costly.

Cunder et al shows that urinary bladder urothelial carcinoma diagnosed by combination of cytoscopy and biopsy with urine cytology as additional technique. The accuracy of urine cytology varies from one pathologist to another & depend upon experience of pathologist. In future new method was introduced for detection of cancer cells in urine. Flow cytometry was used to detect protoporphyrin IX in a model consists of normal bladder transitional epithelial cells . Urine samples of 19 patients with histology proved bladder cancer were examined. Incubation period of one hour in normal bladder cells or TCC cells with HAL results in production of protophorphyrin IX only in TCC cells. Even 5% TCC cells can able detect in mixture of normal/ transitional bladder cells. To test feasibility of method in clinical diagnosis urine samples were measured with comparable. The results show that technique may be feasible for the

detection of bladder cancer cells in urine with advantages of simplicity , reliability and objectivity.

Bladder cancer is the most common malignancy of all genitourinary tumours. Gold standard for non- invasive bladder cancer is urine cytology but senstivity is low.

BLADDER CANCER

Transitional cell carcinoma or urothelial carcinoma accounts for 90% of all primary tumors of bladder.

Most bladder cancers appear as a focal or multifocal expression of widespread abnormality of urothelium, progression of which leads to multicentricity in space and recurrence in time.

Clinical Presentation

Eighty percent of the patients with bladder carcinoma present with gross or microscopic, painless and intermittent hematuria. Twenty percent of patients will complain of vesical irritative symptoms including urinary frequency and urgency. It is important to consider CIS [Carcinoma In Situ.] in any patient with a history of irritative voiding symptoms. Patients with invasive bladder cancer may have abdominal tenderness or bladder mass or induration.

Biologic Pathways

Two distinct pathways are suggested in urothelial neoplasia. A lowgrade pathway hypothesized in approximately 70% the of cases. It is characterized by

progression from hyperplasia/dysplasia to papilloma to low grade transitional cell carcinoma. The lesions have bland cytology and normal blood group isoantigens and are predominantly diploid. Recurrences are frequent and multiple, but only minority of the cases (10 to 15%) progress to muscle invasion

In the high grade pathway most invasive lesions arise without a history of papillary neoplasms. They progress directly from flat lesions of severe dysplasia/carcinoma in situ to invasive high grade transitional cell carcinoma and are associated with mortality. Such lesions have pleomorphic cytology, manifest high mitotic rates,lack normal blood group isoantigens,and are usually aneuploid[11,50].

The flat carcinoma in situ may precede invasive carcinoma by months or years. A primary goal of urine cytology is to recognize these early flat lesions before they invade, as well as to detect the 10% of papillary lesions that are destined to invade[11.]

Cytologic classification of urothelial malignancy

General Principles of Cytologic Diagnosis

Higher the grade and the more extensive the tumor, greater the ability to make a cytologic diagnosis. Cells shed from transitional cell carcinoma in situ have a similar cytomorphology as high-grade invasive lesion. One cannot reliably determine whether a lesion is in situ or invasive cytologically.

***Cellular features of urothelial neoplasia*[50,51]**

Cells	Low grade	High grade
Arrangements	Papillary and loose clusters	Isolated and loose clusters
Size	Increased, uniform	Increased, Pleomorphic
Number	Often numerous	Variable
Cytoplasm	Homogenous	Variable
Nuclear cytoplasmic ratio	Increased	Increased
Nuclei		
Position	Extremely eccentric	Eccentric
Size	Enlarged	Variable
Morphology	Variable within aggregates	Variable
Borders	Irregular	Irregular
Chromatin	Fine	Coarse
Nucleoli	Small	Variable

Differential diagnosis.

Differential Diagnosis includes atypia due to catheterization, cystitis, stones, radiation and chemotherapy.

Differentiating features of reactive cell, low grade and high grade TCC

High nuclear cytoplasmic ratio, irregular nuclear membrane, nonvacuolated cytoplasm are three key features in the diagnosis of low grade transitional cell carcinoma[42]

Differentiating features of Reactive cell, Low grade and High grade TCC[44,50,51]

Feature	Reactive	Low grade TCC	High grade TCC
Groups	Pseudopapillae	Papillae, loose or crowded clusters	Loose clusters/syncitia/single
Cells	Enlarged, pleomorphic variable in number.	Enlarged, relatively uniform, often numerous	Enlarged, pleomorphic
N/C ratio	Normal/increased	Increased(slight to moderate)	Increased(moderate to marked)
Nucleus	Central	Eccentric, enlarged	Eccentric, pleomorphic
Nuclear membrane	Smooth,thick	Slightly irregular, thin	Moderate to markedly irregular
Chromatin	Fine, even	Granular, even	Coarse, dark, irregular
Nucleoli	Often large	Small to none	Macronucleoli in many cells
Cytoplasm	Vacuolated	Homogenous	Often vacuolated also squamous
Background	Inflamed or clean	Clean	Diathesis

Dysplasia

Dysplasia describes a flat, non-invasive premalignant lesion distinguished from reactive or reparative epithelium. The cytologic diagnosis of urothelial dysplasia is a point of contention. The cells are reported to have a lesser degree of cytologic atypia than transitional cell carcinoma in situ but are similar in appearance to cells from low-grade papillary neoplasms. The chief differences are the small number of dysplastic cells present in urinary specimens, the aggregation of cells into small but loose clusters, a lower N/C ratio [Nuclear

Cytoplasmic ratio] and fine evenly distributed chromatin. In truth urothelial dysplasia cannot reliably be segregated from low-grade TCC with subjective criteria of cytology alone.

Papilloma

Papillomas are well-differentiated papillary transitional cell neoplasms. Many papillomas are composed of cells with normal or nearly normal morphologic appearance, making cytologic diagnosis difficult or impossible. Others have morphologic feature of low grade neoplasm. Therefore only 1/3rd to 2/3 rd of these lesions can be diagnosed cytologically and the higher diagnostic yield (fewer false negatives) comes at the expense of more false positive diagnosis[50].

Numerous cells may be exfoliated. Loose clusters and papillary aggregates commonly occur, but must be differentiated from pseudopapillary clusters related to trauma, instrumentation, stones, etc. True papillary fronds with fibrovascular cores are diagnostic of papillary neoplasia. However, their presence is not essential for cytologic diagnosis. The cells and their nuclei are larger than normal deep transitional cells (but not superficial cells). The cell borders are often indistinct. The cytoplasm is homogeneous rather than vacuolated. The nuclei are eccentric and have slightly irregular membranes in the form of notches or creases. The chromatin is fine and evenly distributed. Nucleoli, if present, are small[50,51].

Carcinoma in Situ:

A lesion in which transitional epithelium, of variable thickness, is composed of variably sized abnormal cells with significant nuclear and cytoplasmic abnormalities, limited to the epithelium and never crosses the basal layer.

Squamous Cell Carcinoma

Squamous cell carcinoma can be accurately identified from cells in urine sample. They are usually well differentiated and exfoliate fairly mature cells with an elongated, spindled or fusiform configuration. Cytoplasmic keratinization can often be distinguished. Nuclear border is irregular. Nuclear deformation is common.

Adenocarcinoma

Primary adenocarcinomas are rare in the bladder. The adenocarcinoma cells tend to cluster and have poorly stained, lucent, vacuolated cytoplasm. Chromatin tends to aggregate along smooth nuclear borders and manifests. Nucleoli are prominent.

Diagnostic correlation between cytologic and cystoscopic examination[37].

Cytology	Cystoscopy	Likely diagnosis
(-)	**(-)**	No tumor
(-)	(+)	Well differentiated papillary neoplasm
(+)	**(-)**	Carcinoma in situ (or) upper tract tumor.
(+)	(+)	High grade, invasive TCC

Transabdominal ultrasonography has also been used to complement urine cytology in the detection of bladder tumors.

Pitfalls in urinary cytology

- Over interpreting cells with low N/C ratio [Nuclear Cytoplasmic ratio] as
- Cancer cells.
- Mistaking papillary aggregates as a reliable sign of low grade neoplasia
- Confusing the reactive/regenerative/reparative cell associated with urinary

  Stones with neoplastic cells.
- Over interpreting samples from the upper collecting system.
- Misinterpreting cells in ileal conduits and
- Misunderstanding the cytologic effects of drugs and X ray therapy.

Morphologic features

TCC [Transitional Cell Carcinoma] can arise any where in the bladder.

Common locations are:

Lateral walls 37%

Posterior wall 18%

Trigone 12%

Neck 11%

Ureteric orifices 10%

Dome 8% and

Anterior wall 4%

Pattern of growth may be exophytic or endophytic or a combination of both. Exophytic tumor may adopt a papillary configuration (with central fibrovascular core) or a solid appearance (nodular). Exophytic tumor results in clusters of tumor cells in the lamina propria which may be under diagnosed as Von Brunn's nests or cystitis glandularis or cystica. This is referred to as the nested variant of transitional cell carcinoma.

Stromal invasion by transitional cell carcinoma proceeds in two stages. Invasion of the lamina propria and invasion of muscle layer. Muscle invasion is of great consequence because of its influence on therapy and prognosis. Care should be exercised not to misinterpret the inconsistent but sometimes prominent fascicles of muscularis mucosa as belong to the muscularis propria.

It is also important not to misinterpret the mature adipose tissue commonly present in the lamina propria or muscularis propria as perivascular soft tissue, in order to avoid a tumor adjacent to fat in a biopsy specimen being badly overstaged.

The cyto architectural variations that may occur in transitional cell carcinoma are

1. Foci of glandular metaplasia are common, usually in the form of intra-cytoplasmic mucin containing vacuoles.
2. Foci of squamous differentiation especially in high grade tumors may be seen.

3. Clear cells may be prominent in transitional cell carcinomia and simulate adenocarcinoma.
4. Micropapillary pattern may occur which resembles that of ovarian serous papillary carcinoma.
5. Rare variant of TCC is characterized by a plasmacytoid appearance that mimics myeloma.

Bladder Biopsy

Transurethral Resection

Before tumors are resected, their location, number and size should be noted. Endoscopically visualised characterization with predictive value for disease progression include shape (papillary versus sessile and flat), size (less than 2 cm versus greater than 5 cm) and the presence of associated mucosal abnormalities.

Kenneth B. Cummings et al[21] suggested hot loop resection of the tumor, after adequate biopsy mapping of bladder mucosa. He also insisted that the resection must include sufficient muscle to allow adequate pathologic staging. As an adjunct to hot loop resection, a cold up biopsy of the tumor edge or base can provide muscle for pathologic staging while reducing charring artifact and the risk of bladder perforation. Video cystoscopy, combined with continuous-flow resectoscope, will allow safe resection in almost all cases.

Grading and Staging

Grading of urothelial tumors[18].

WHO/ISUP Grades (World Health Organization/International Society of Urological

Pathology). Adopted as WHO system in 2004.

Urothelial papilloma

Urothelial neoplasm of low malignant potential

Papillary Urothelilal Carcinoma, low grade

Papillary Urothelial Carcinoma, high grade.

WHO Grades (1973)

Urothelial Papilloma

Urothelial neoplasm of low malignant potential

Papillary Urothelial Carcinoma, Grade 1

Papillary Urothelial Carcinoma, Grade 2

Papillary Urothelial Carcinoma, Grade 3

Histologic feature used to classify Urothelial Papillary lesions according to the scheme proposed by the WHO/ISUP [The World Health Organization / International Society of Urological Pathology][19].

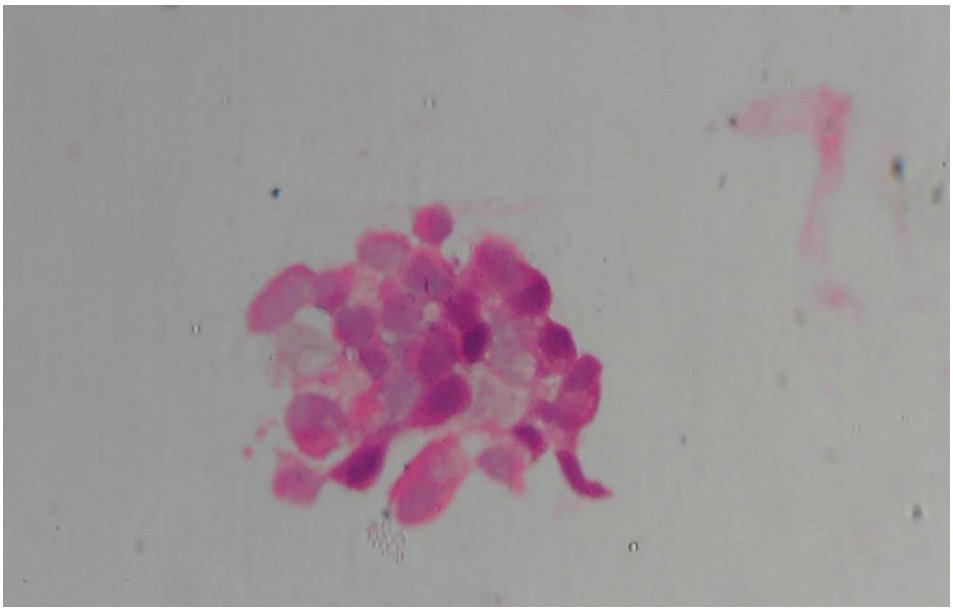
Architecture	Papilloma	Papillary neoplasm of low malignant potential	Low grade Papillary Carcinoma	High grade Papillary Carcinoma
Papillae	Delicate	Delicate, Occasionally Fused	Fused, branching and delicate	Fused, branching and delicate
Organization of cells	Identical to normal	Polarity identical to normal; any thickness; cohesive	Predominantly ordered, yet minimal crowding and minimal loss of polarity; any thickness; cohesive	Predominantly disordered with frequent loss of polarity, any thickness; often discohesive

.

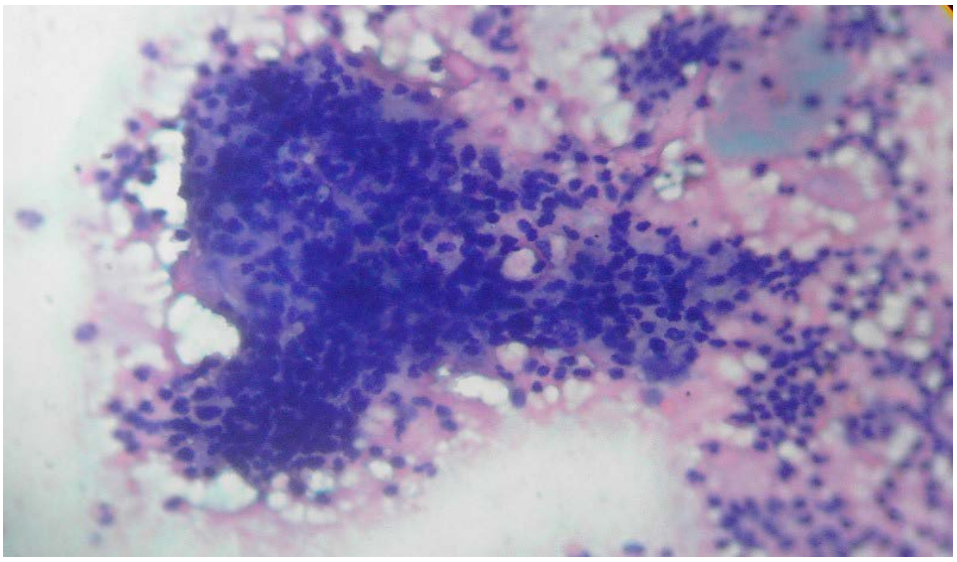
Histologic feature used to classify Urothelial Papillary lesions according to the scheme proposed by the WHO/ISUP [The World Health Organization / International Society of Urological Pathology][19].

Cytology				
Nuclear size	**Identical to normal**	**May be uniformly enlarged**	**Enlarged with variation in size**	**Enlarged with variation in size**
Nuclear shape	Identical to normal	Elongated, roundoval, Uniform	Round-oval; slight variation in shape and contour	Moderatemarked Pleomorphism.
Nuclear Chromatin	Fine	Fine	Mild variation within and between cells.	Moderatemarked variation both within and between cells with hyperchromasia.
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous*	Multiple Prominent nucleoli may be present
Mitosos	Absent	Rare, basal	Occasional, at any level	Usually frequent at any level

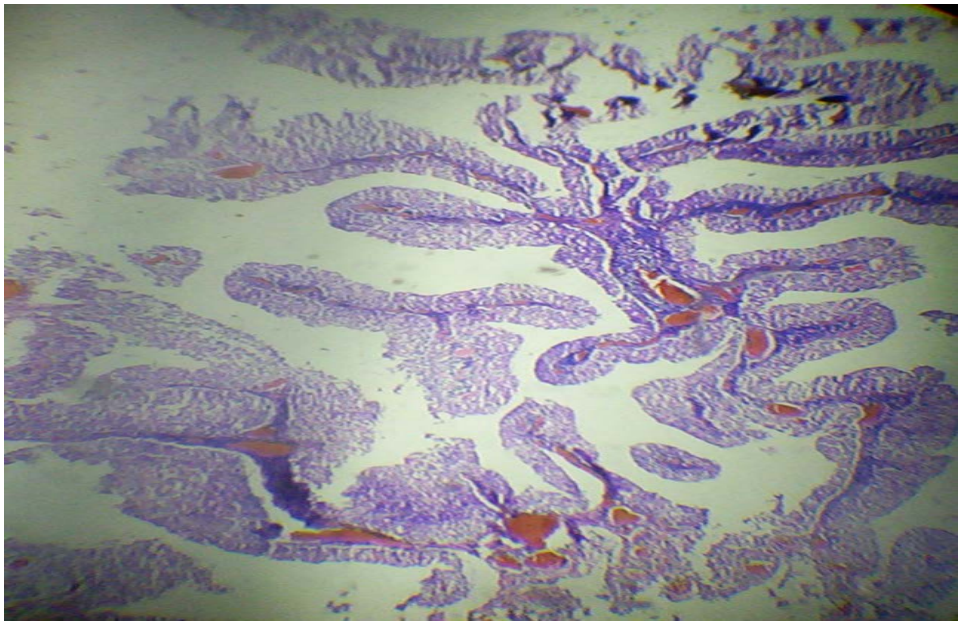
URINE CYTOLOGICAL PICTUTRE



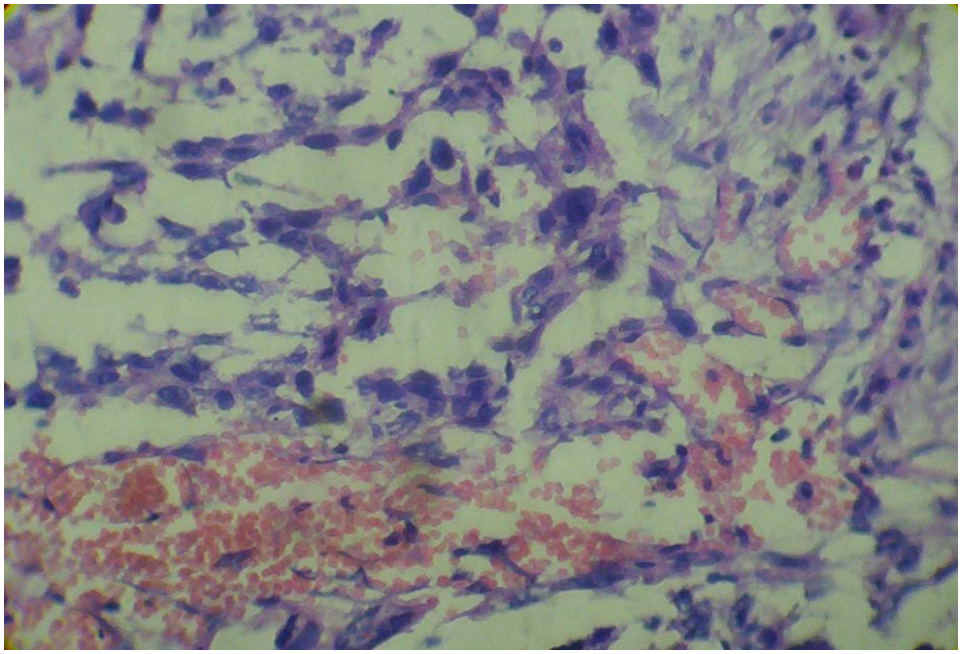
Urine sediment smaer shows degenerated cells groups shoeing vacuolated Cytoplasm and degenerated nuclei. H&E Stain (400x)



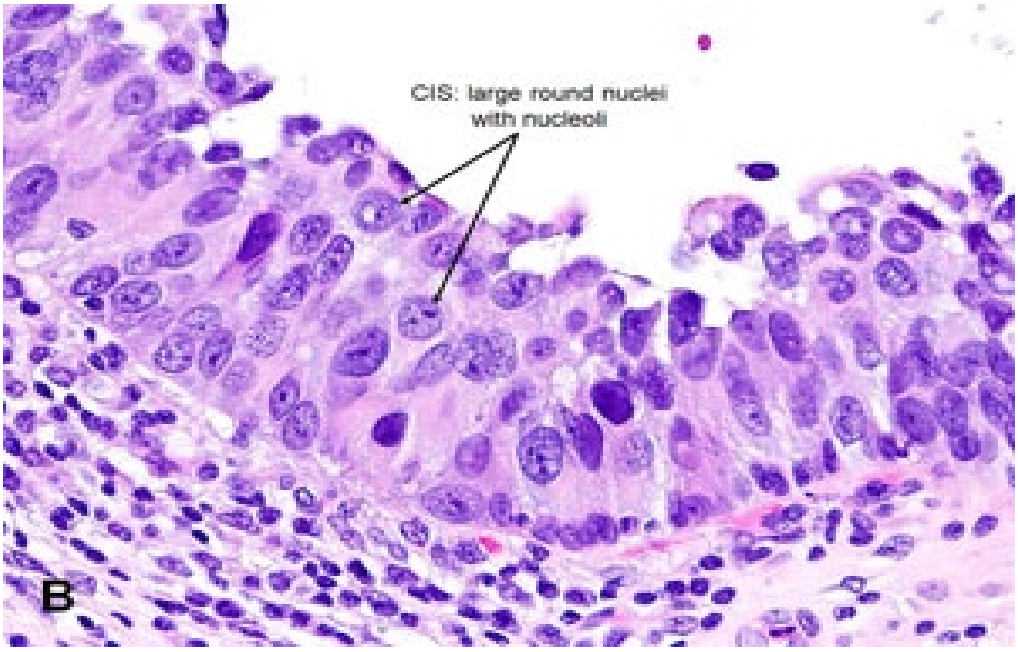
Urine sediment smear of low grade TCC. Papstain (400X).



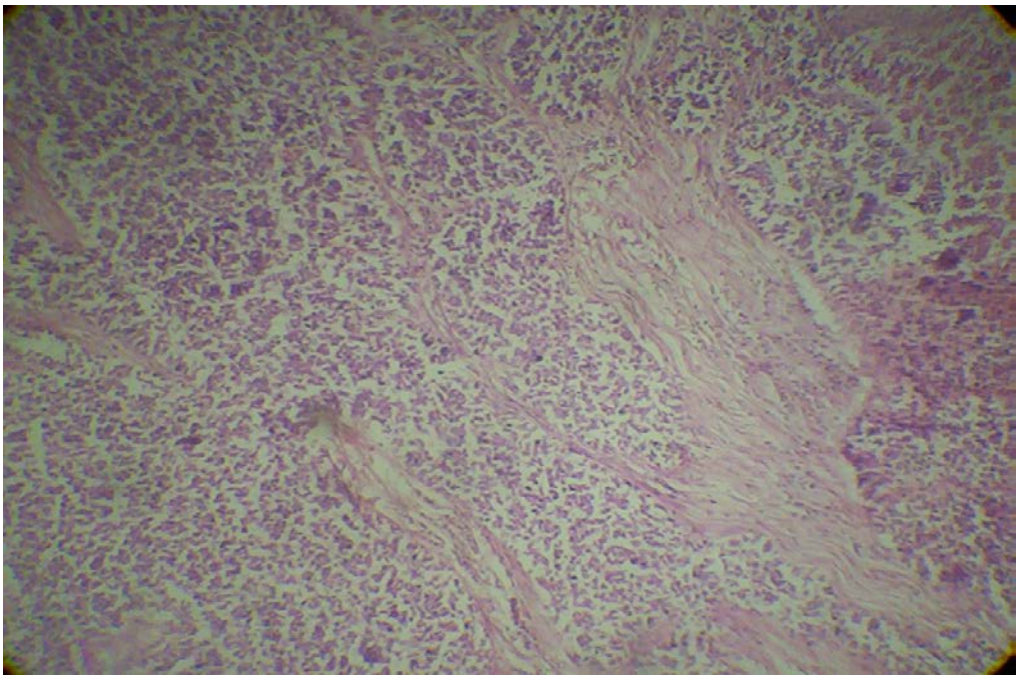
Histology of lowgrade papillary TCC showing branching, delicate papillae



Histology of High grade papillary TCC showing cells with pleomorphic hyperchromatic nuclei . H & E. (400)



Histology shows carcinoma in situ



Histology shows muscle invasion in TCC . H & E stain (400)

Pathologic T (Primary tumor) staging of bladder carcinoma[18].

AJCC/UICC	Depth of invasion
Non invasive, Papillary	Ta
Carcinoma in situ(Non invasive, flat)	Tis
Lamina Propria invasion	T1
Muscularis Propria invasion	T2
Microscopic extravesicle invasion	T3a
Gross apparent extravesicle invasion	T3b
Invades adjacent structures	T4

Regional Lymph Nodes (N)

NX Lymph nodes cannot be assessed

N0 No lymph node metastasis

N1 Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)

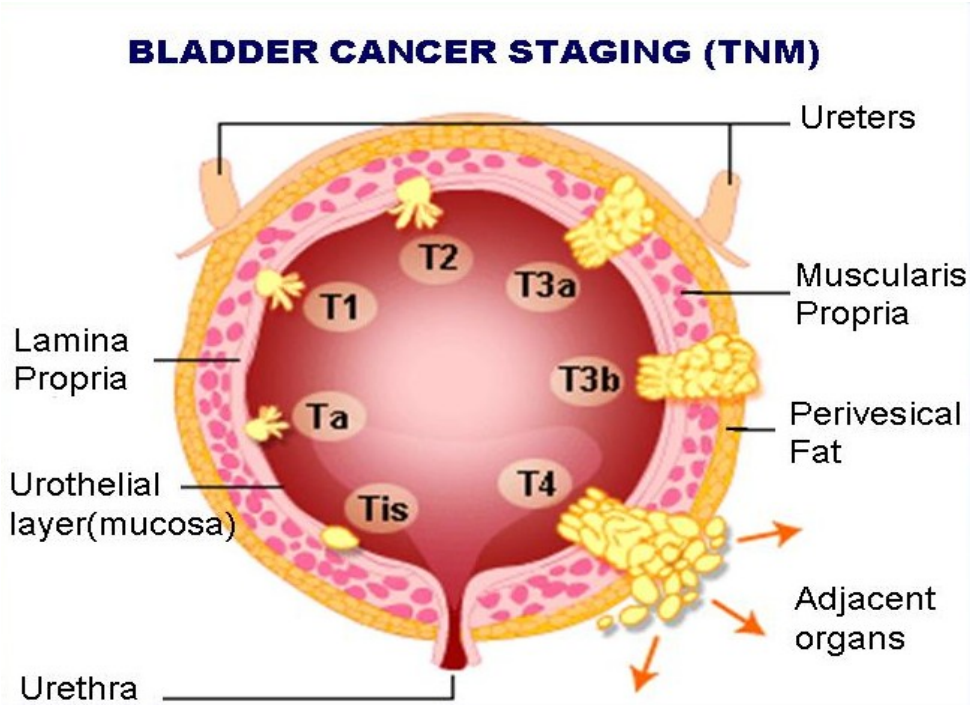
N2 Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)

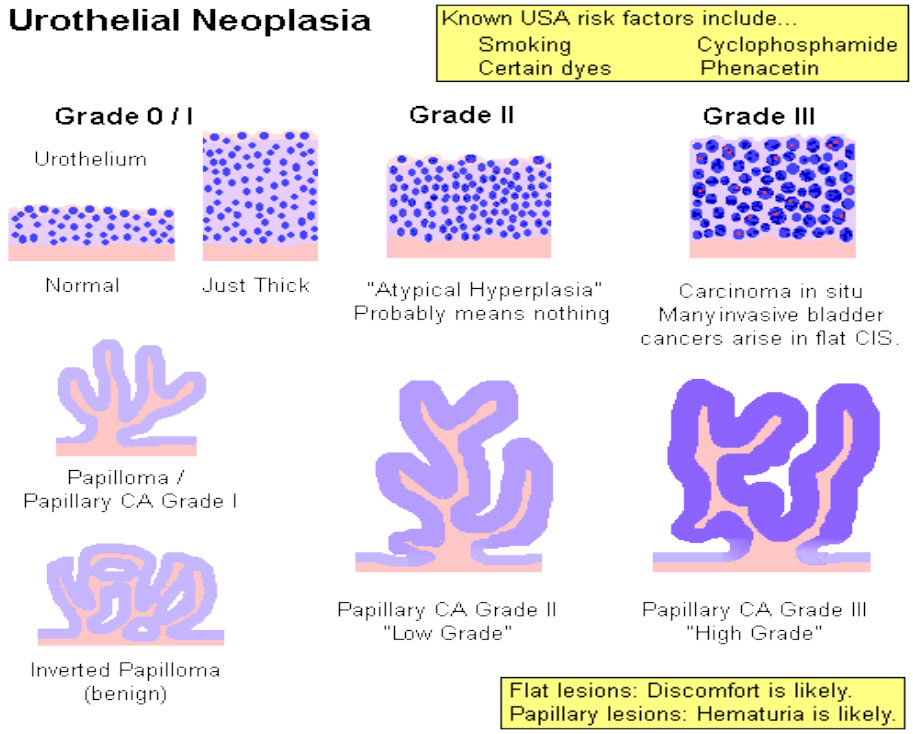
N3 Lymph node metastasis to the common iliac lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis


BLADDER CANCER STAGING (TNM)
Ureters
T2
T3a
T1
Muscularis Propria
Lamina Propria
T3b
Ta
Perivesical Fat
Urothelial layer(mucosa)
T4
Tis
Adjacent organs
Urethra


Urothelial Neoplasia
Known USA risk factors include...
Smoking
Certain dyes
Cyclophosphamide
Phenacetin
Grade 0 / I
Grade II
Grade III
Urothelium
Normal
Just Thick
"Atypical Hyperplasia"
Probably means nothing
Carcinoma in situ
Many invasive bladder cancers arise in flat CIS.
Papilloma / Papillary CA Grade I
Inverted Papilloma (benign)
Papillary CA Grade II
"Low Grade"
Papillary CA Grade III
"High Grade"
Flat lesions: Discomfort is likely.
Papillary lesions: Hematuria is likely.

Ultrasonography

The most common sonographic appearance of TCC is hypoechoic mass in the renal collecting system that splits the central echocomplex with varying degrees of infundibular dilatation. Focal hypoechogenicity of adjacent renal cortex reflects local invasion. Occasionally, the central echocomplex may be only segmentally amputated.

Ultrasonography is inaccurate for diagnosing early TCC, useful in the diagnosis of obstructive uropathy. Ureteric lesions are particularly difficult to visualize unless they cause hydronephrosis and hydroureter. The other limitation of ultrasonography is that it is inaccurate in the staging of bladder TCC, particularly Ta and T1 tumors, and also in the detecton of pelvic lymph node involvement.

On sonograms, calculi may be confused with high-grade TCCs, which can be densely echogenic. No sonographic features are specific for TCC, and many filling defects within the renal collecting system and bladder may have a nonspecific appearance. In addition, ultrasonography is limited in its capacity to depict nondilated ureters.

Local spread and metastasis

Bladder carcinoma may extend into the ureters, neck of the bladder, urethra, prostatic ducts and seminal vesicle.

Lymphnode metastasis in the pelvic chains are found in 25% of invasive tumors. The most common sites of distant metastatis are the lungs, liver, bone and central nervous system.

Histochemical and Immunohistochemical features.

The co-ordinate expression of CK7 and CK20 is a feature of transitional cell carcinoma. CK20 positivity is common and strong in the high grade tumors. Thrombomodulin and Uroplakin III are two new useful markers for transitional cell carcinomia, but the former is not very specific and the later is only moderately sensitive.

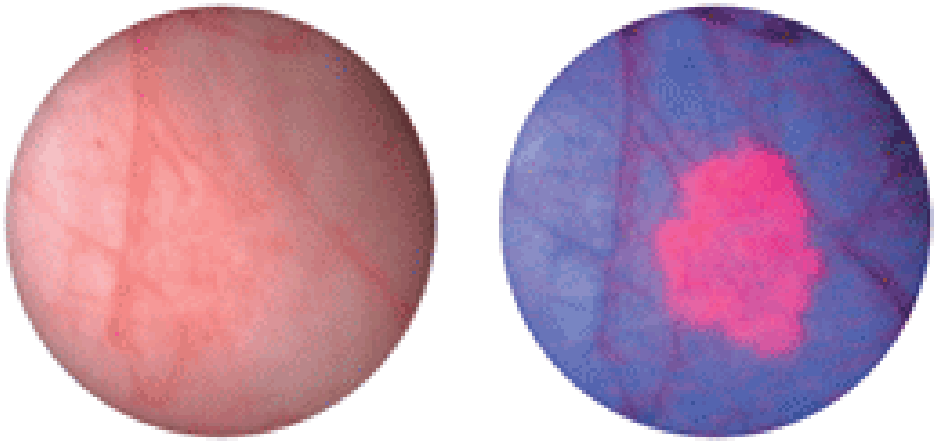
Other markers commonly expressed by these tumors are CEA and cathepsin B (high grade tumors), CA19-9, CD15 (leu M1), survivin and androgen receptors. Deletion of ABO blood group antigen is a common finding in transitional cell carcinomas particularly in high grade tumors.

Staining for the basal lamina component laminin has been advocated for the detection of early stromal invasion. Tenascin an extra-cellular matrix protein is strongly expressed in invasive, high-grade carcinomas with abundant stroma and is thought to reflect both the severity of the inflammatory infiltrate and the extent of stromal remodel

ULTRASOUND PICTURE IN CA BLADDER

Ultrasound shows multiple, sessile muscle invasive tumours (Hyperechoic)

CYSTOSCOPIC PICTURE



Cystoscopy shows red, velvety lesions (CIS), well seen after fluorescence cystoscopy

MATERIALS AND METHODS

MATERIALS AND METHODS

1.Study group :

70 Patients who were admitted in Department of Urology, Kilpauk Medical College and Govt. Royapettah Hospital in coordination with Department of Pathology, patients presented with lower urinary tract symptoms (LUTS) due to bladder transitional cell carcinoma detected by ultrasonography were included in the study

2.Study design : Prospective clinical study

3.Study period : One Year from January 2014 to January 2015

4.Materials :

Freshly voided urine samples are collected for cytological examination. Cystoscopy was performed in all patients using rigid cystoscope and details of growth are noted. Material was obtained from TURBT biopsy , Radical Cystectomy specimen

Freshly voided urine samples are collected usually 3 hours after first morning void. Samples are immediately mixed with 95 % alcohol and kept in refrigerator till centrifuged. Approximately 100ml of urine are centrifuged at 2500 revolution/min for 20 min. Multiple smears are prepared from sediment and slides are fixed in 95% alcohol immediately.

Smears are stained with papanicolaou stain and haematoxylene and eosin stain. Interpretation of exfoliative cytology of urinary sediments are classifieds as Negative, Atypia, Suspcious, Positive

Biopsies taken are processed routinely and 3-5 u thick sections are cut. H & E Staining was done on tissue section for morphological evaluation & lesions are histologically classified as Low grade, High grade & No malignancy

Inclusion criteria

- Patients with Bladder Neoplasms detected by ultrasound
- Symptomatic patients with LUTS and hematuria

Exclusion criteria

- Patients who already undergone biopsy
- Other causes of Hematuria like RCC, Upper tract TCC

Statistical Analysis was performed with **Statisticial Package for the Social Sciences (SPSS**) Version 15 software using Pearson's Chi-Square Test and Fischer's Exact Test with $P < 0.05$ considered to indicate statistical significance

OBSERVATION AND RESULTS

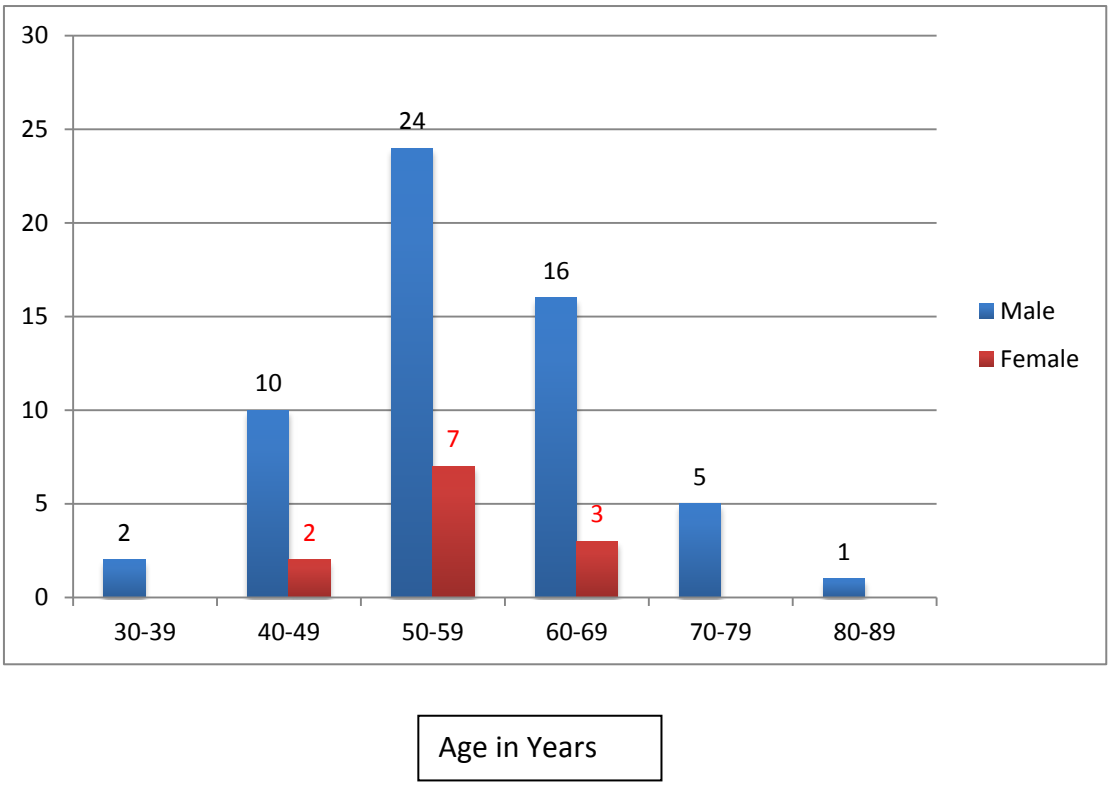
70 patients of urinary bladder neoplasms diagnosed by ultrasonography were studied for comparative evaluation of urinary cytology with Histopathological correlation. The findings in these patients have been presented as

- Clincal Data
- Ultrasonography and Cystoscopic Findings
- Cytology and Histopathological Report

Table : 1 Age /Sex wise Distribution

AGE	MALE	FEMALE
30-39	2	-
40-49	10	2
50-59	24	7
60-69	16	3
70-79	5	-
80-89	1	-

CHART 1: Age /Sex wise Distribution

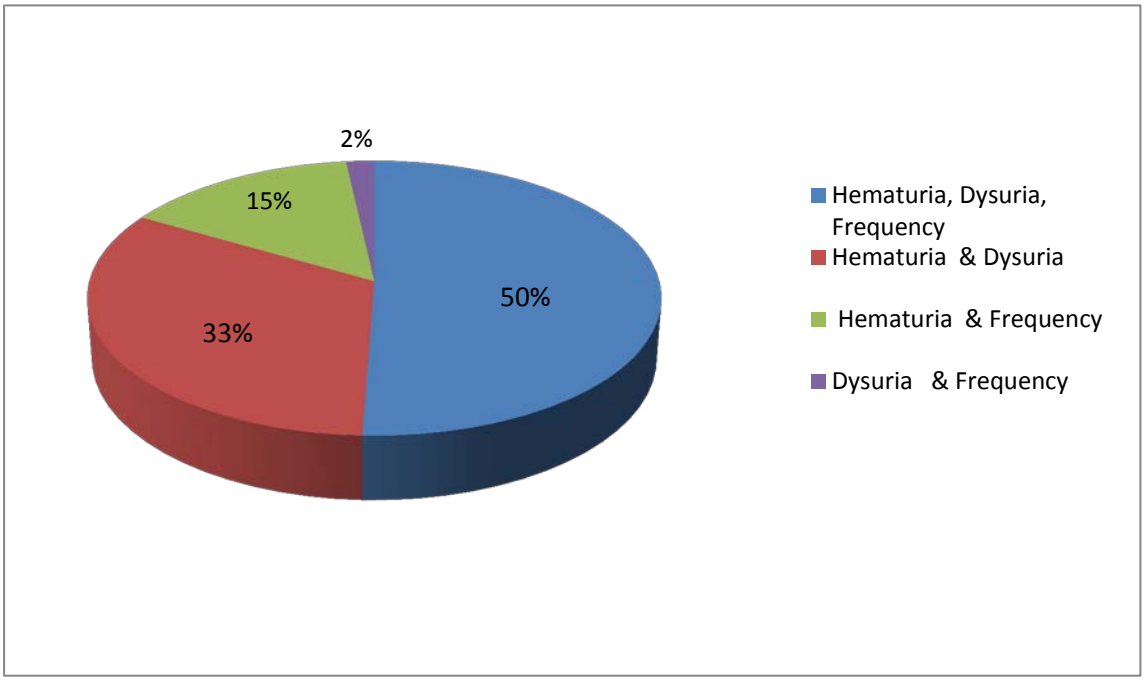


Among our study group, Most common Age Group – 50-59 Years (42%). Male to Female Ratio was 4:1. Since age and Sex distribution are not statistically significant (>0.05), it means that there is no difference between the Urine Cytology Findings groups. In other words the groups contain subjects with the same basic demographic characteristics

TABLE 2: CLINICAL FEATURES

CLINICAL PRESENTATION	NO OF PATIENTS
Hematuria, Dysuria, Frequency	34
Hematuria & Dysuria	22
Hematuria & Frequency	10
Dysuria & Frequency	4

CHART 2: CLINICAL FEATURES

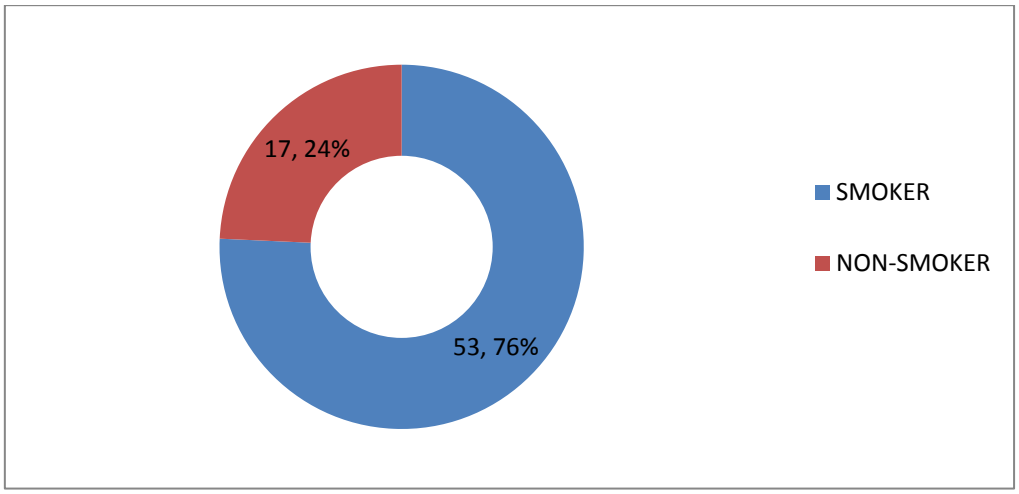


By conventional criteria, association between Clinical Features Distribution and Urine Cytology Findings is considered to be not statistically significant since p 0-936.

TABLE :3 SMOKING HISTORY

SMOKING HISTORY	NO OF PATIENTS	PERCENT
Smoker	53	74%
Non- Smoker	17	26%
Total	70	100%

CHART :3 SMOKING HISTORY



Statisticial Analysis

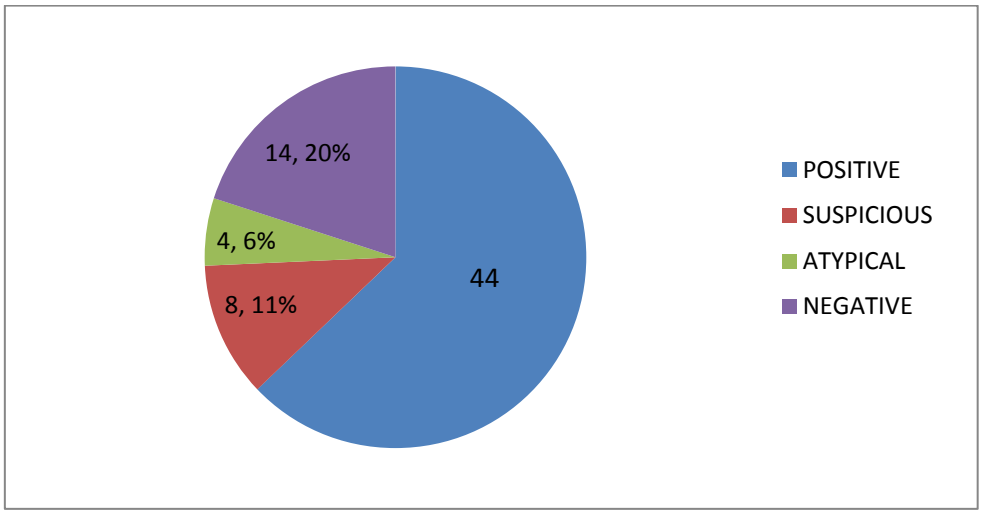
Smoking	Urine Cytology -ve	%	Urine Cytology +ve	%
Smoking -ve	6	33.33	11	21.15
Smoking +ve	12	66.67	41	78.85
Total	18	100.00	52	100.00
Chi Square Statistic			1.08	
Degrees of Freedom			1	
P value Chi Square Test			0.299	

By conventional criteria the association between Smoking Status and Urine Cytology Findings is considered to be not statistically significant since $p > 0.05$.

TABLE : 4 URINE CYTOLOGY

URINE CYTOLOGY RESULTS	NO OF CASES
POSITIVE	44
SUSPICIOUS	8
ATYPICAL	4
NEGATIVE	14

CHART :4 URINE CYTOLOGY

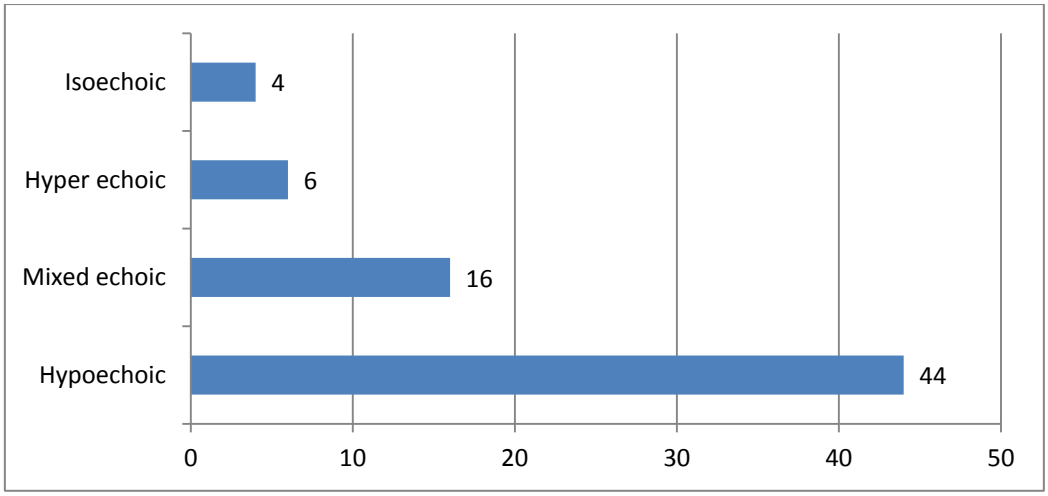


In our study group, urine cytology were positive for cancer cells in 44(63 %), Suspicious in 8, (11%), Atypical in 4 (6%), Negative in 14(20%) patients

TABLE : 5 ULTRASONOGRAPHIC FINDINGS

TYPE OF LESION	NO OF CASES	PERCENTAGE
HYPOECHOGENIC	44	60%
MIXED ECHOIC	16	17%
HYPERECHOIC	6	8%
ISOECHOIC	4	5%
TOTAL	**70**	**100%**

CHART : 5 ULTRASONOGRAPHIC FINDINGS



Statisticial Analysis

Ultrasound Findings	Urine Cytology -ve	%	Urine Cytology +ve	%
Hypoechogenic	8	44.44	36	69.23
Mixed Echoic	6	33.33	10	19.23
Hyperechoic	4	22.22	2	3.85
Isoechoic	0	0.00	4	7.69
Total	18	100.00	52	100.00
Chi Square Statistic			9.12	
Degrees of Freedom			3	
P value Chi Square Test			0.028*	

By conventional criteria the association between Ultrasound Findings and Urine Cytology Findings is considered to be statistically significant since $p < 0.05$

CHART 6: LOCATION OF LESIONS IN CYSTOSCOPY

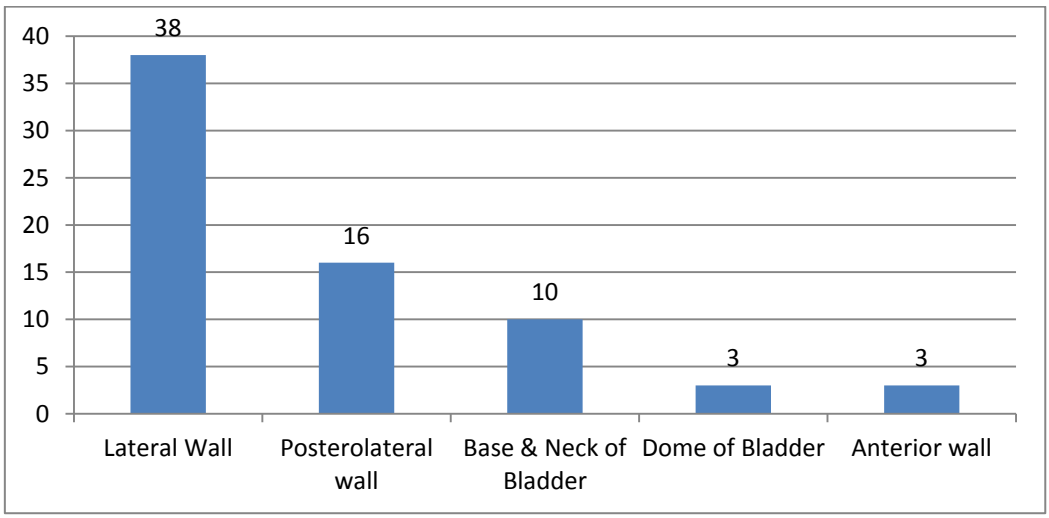


Table 6: Statitiscial Analysis

Location of Lesions	Urine Cytology -ve	%	Urine Cytology +ve	%
Lateral Wall	12	66.67	26	50.00
Posterolateral Wall	3	16.67	13	25.00
Base & Neck ofBladder	2	11.11	8	15.38
Dome of bladder	1	5.56	2	3.85
Anterior Wall	0	0.00	3	5.77
Total	18	100.00	52	100.00
Chi Square Statistic			2.39	
Degrees of Freedom			4	
P value Chi Square Test			0.664	

By conventional criteria the association between Location of Lesions and Urine Cytology Findings is considered to be not statistically significant since $p > 0.05$.

CHART 7 : TYPE OF LESIONS IN CYSTOSCOPY

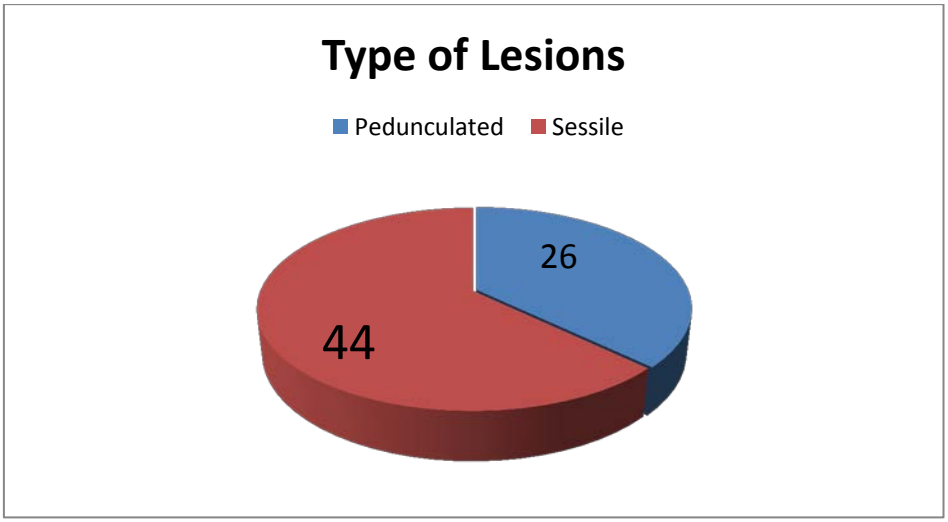


Table7 : Statisticial Analysis

Type of Lesions	Urine Cytology -ve	%	Urine Cytology +ve	%
Pedunculated	9	50.00	17	32.69
Sessile	9	50.00	35	67.31
Total	18	100.00	52	100.00
Chi Square Statistic			1.72	
Degrees of Freedom			1	
P value Chi Square Test			0.190	

By conventional criteria the association between Type of Lesions and Urine Cytology Findings is considered to be not statistically significant since p > 0.05.

CHART 8: NUMBERS OF TUMOURS IN CYSTOSCOPY

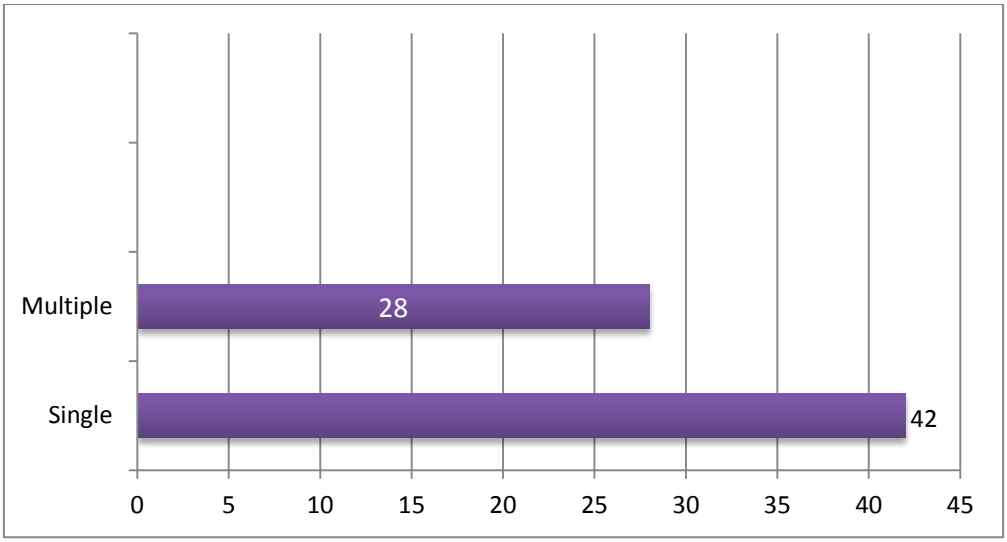


Table 8: Statisticial Analysis

No of Tumours	Urine Cytology -ve	%	Urine Cytology +ve	%
Single	10	55.56	32	61.54
Multiple	8	44.44	20	38.46
Total	18	100.00	52	100.00
Chi Square Statistic			0.199	
Degrees of Freedom			1	
P value Chi Square Test			0.655	

By conventional criteria the association between Number of Tumours and Urine Cytology Findings is considered to be not statistically significant since p > 0.05.

Chart 9 : SIZE OF TUMOUR AT CYSTOSCOPY

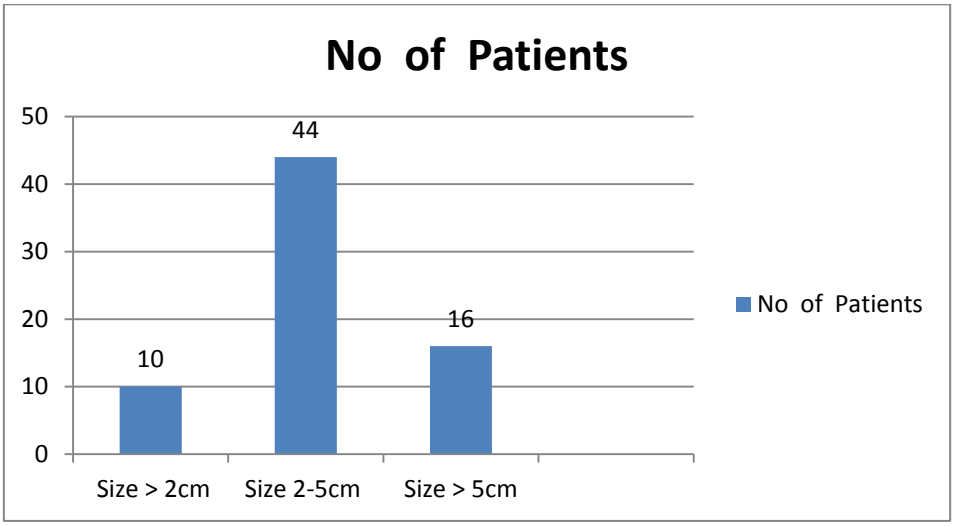
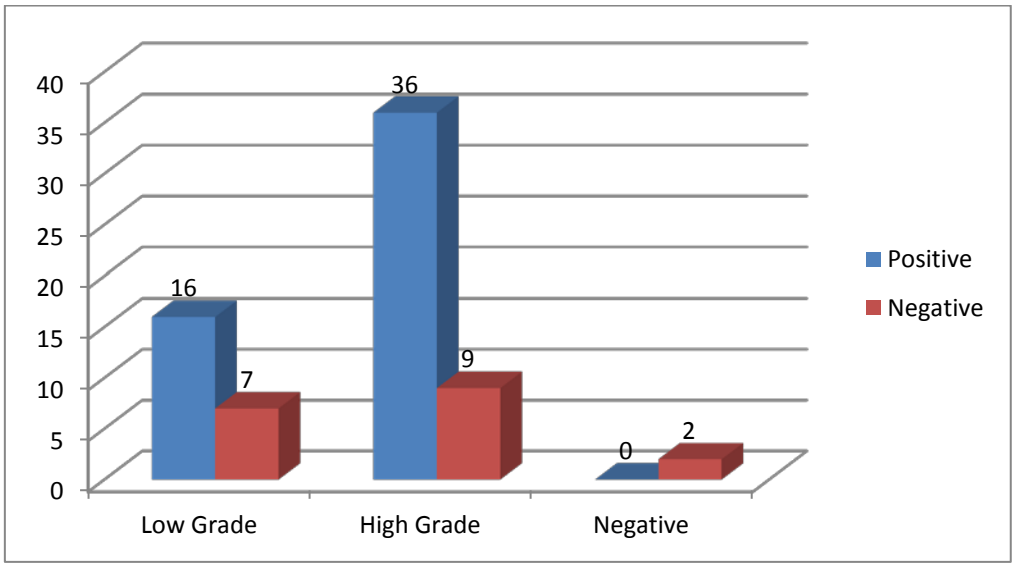


TABLE 10: COMPARISON OF HISTOLOGY WTIH URINARY CYTOLOGY

HISTOLOGY	CYTOLOGY		TOTAL
	POSITIVE	NEGATIVE	
LOW GRADE	16	7	23
HIGH GRADE	36	9	45
NEGATIVE	0	2	2
TOTAL	**52**	**18**	**70**

CHART 10 : COMPARISON OF HISTOLOGY WTIH URINARY CYTOLOGY



Statistical Analysis

Histological Diagnosis	Urine Cytology -ve	%	Urine Cytology +ve	%
Negative	2	11.11	0	0.00
Low Grade	7	38.89	16	30.77
High Grade	9	50.00	36	69.23
Total	18	100.00	52	100.00
Chi Square Statistic			6.82	
Degrees of Freedom			2	
P value Chi Square Test			0.033*	

P value - Significant

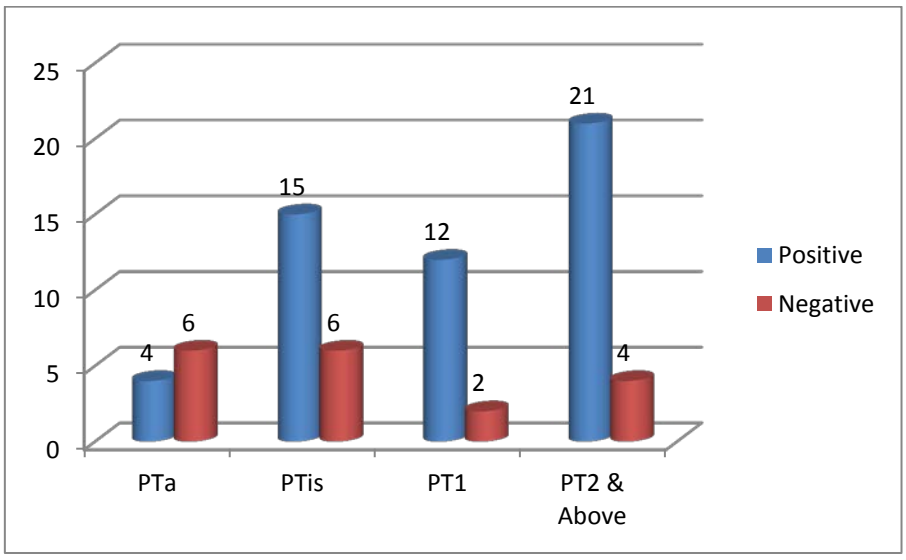
Statistical Significance

- In simple terms, the incidence of High Grade Histological Positivity is 50% in Urine Cytology –ve Group compared to 69.23% in Urine Cytology +vegroupwith a p-value of 0.033 according to Chi-Squared test.
- This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance.

TABLE 11: COMPARISON OF URINARY CYTOLOGY WITH TUMOUR STAGING

URINE CYTOLOGY	PTa,	PTis	PT1	PT2 & Above
Positive	4	15	12	21
Negative	6	6	2	4
Total	**10**	**21**	**14**	**25**

CHART 11: COMPARISON OF URINARY CYTOLOGY WITH TUMOUR STAGING



Statisticial Analysis

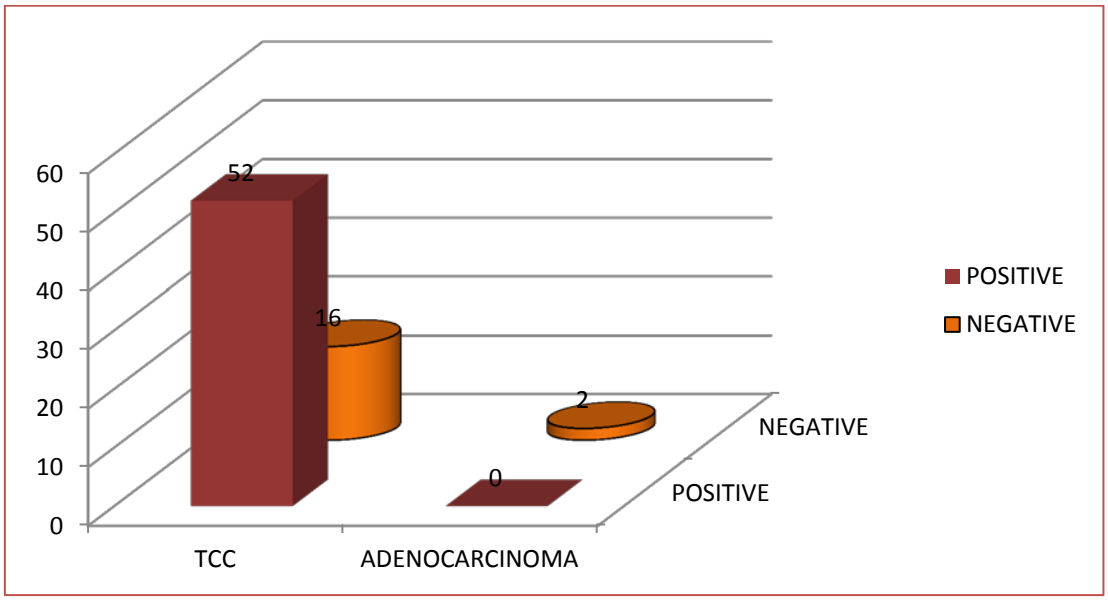
Tumour Staging	Urine Cytology -ve	%	Urine Cytology +ve	%
Pta	6	33.33	4	7.69
Ptis	6	33.33	15	28.85
PT1	2	11.11	12	23.08
PT2 & Above	4	22.22	21	40.38
Total	18	100.00	52	100.00
Chi Square Statistic			8.44	
Degrees of Freedom			3	
P value Chi Square Test			0.038*	

By conventional criteria the association between Tumour Staging and Urine Cytology Findings is considered to be statistically significant since $p < 0.05$.

TABLE :12 COMPARISON OF URINE CYTOLOGY WITH DIFFERENT HISTOLOGY

HISTOLOGY	URINARY CYTOLOGY	
	POSITIVE	NEGATIVE
TCC	52	16
ADENOCARCINOMA	0	2
TOTAL	52	18

CHART 12: COMPARISON OF URINE CYTOLOGY WITH DIFFERENT HISTOLOGY



Statistical Analysis

Type of Tumour	Urine Cytology -ve	%	Urine Cytology +ve	%
TCC	16	88.89	52	100.00
Adenocarcinoma	2	11.11	0	0.00
Total	18	100.00	52	100.00
Chi Square Statistic			5.95	
Degrees of Freedom			1	
P value Chi Square Test			0.015*	

By conventional criteria the association between Types of Tumour and Urine Cytology Findings is considered to be statistically significant since $p < 0.05$.

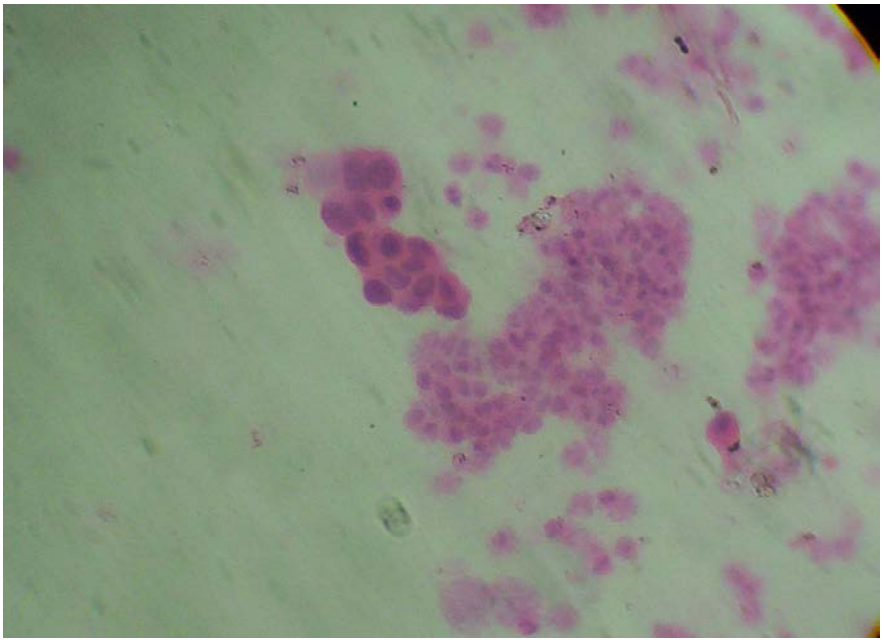
Accuracy Statistics

Histological Diagnosis	Positive	Negative	Total
Urine Cytology +ve	52	0	52
Urine Cytology -ve	16	2	18
Total	68	2	70

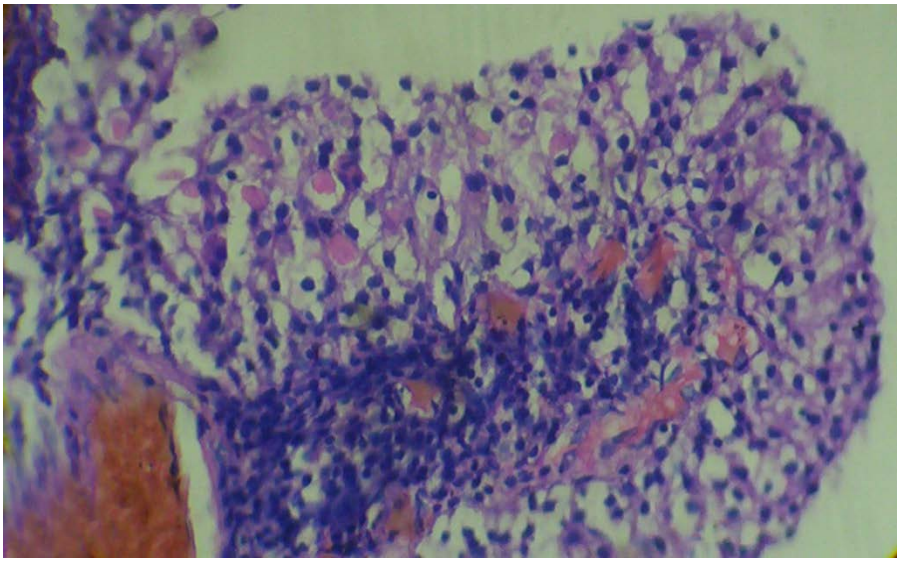
Accuracy Statistics	
Sensitivity	96%
Specificity	26%
Positive Predictive Value	76.5%
Negative Predictive Value	90%
Likelihood Ratio +ve	1.13
Likelihood Ratio -ve	0.00
Diagnostic Effectiveness	0.77
Prevalence	0.74

- Sensitivity of Urine Cytology study findings is High, meaning that malignancy +ve test result often occurs in those with malignancy
- Specificity of Urine Cytology study findings is extremely low, meaning that malignancy –ve test very rarely occurs in those without malignancy
- The diagnostic effectiveness or diagnostic accuracy is very high. It means that the overall value of Urine Cytology studyin detecting malignancy as a combined screening and case-finding test is good
- Prevalence of this condition is very common

CYTOLOGICAL PICTURE

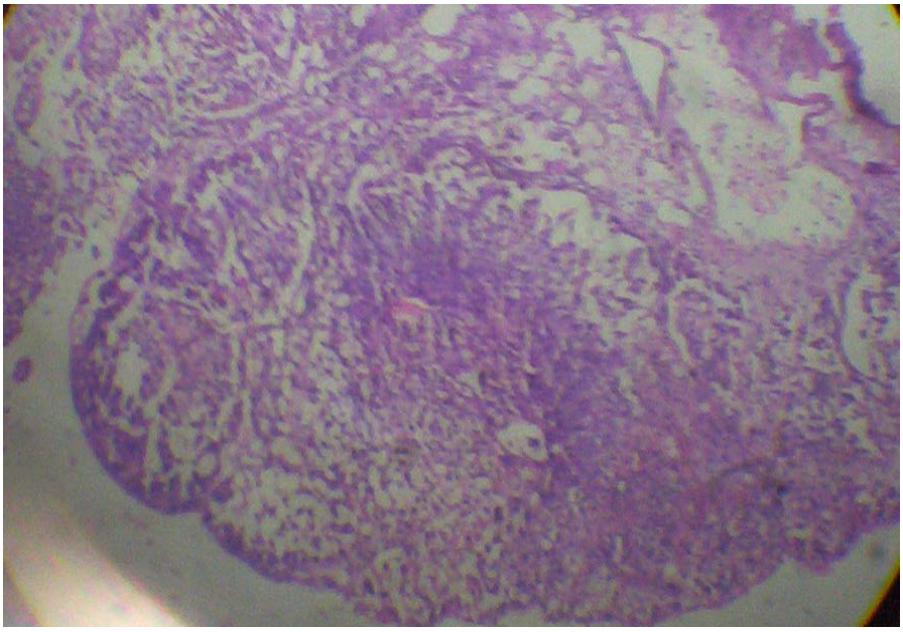


Urine sediment smear of low grade TCC. H&E (400X)

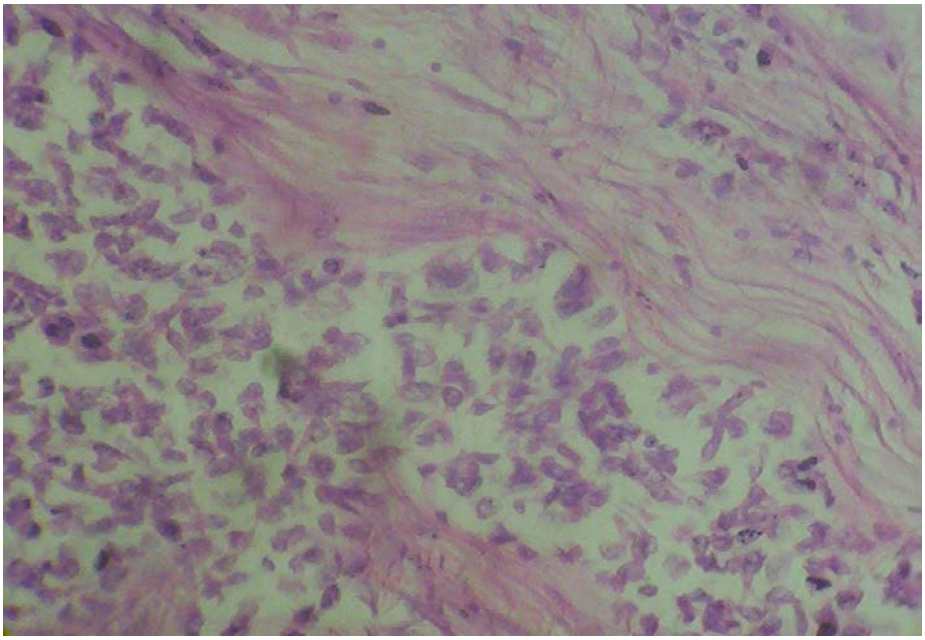


Histology of low grade papillary TCC showing papillary structure with orderly arranged cells. H&E. (400)

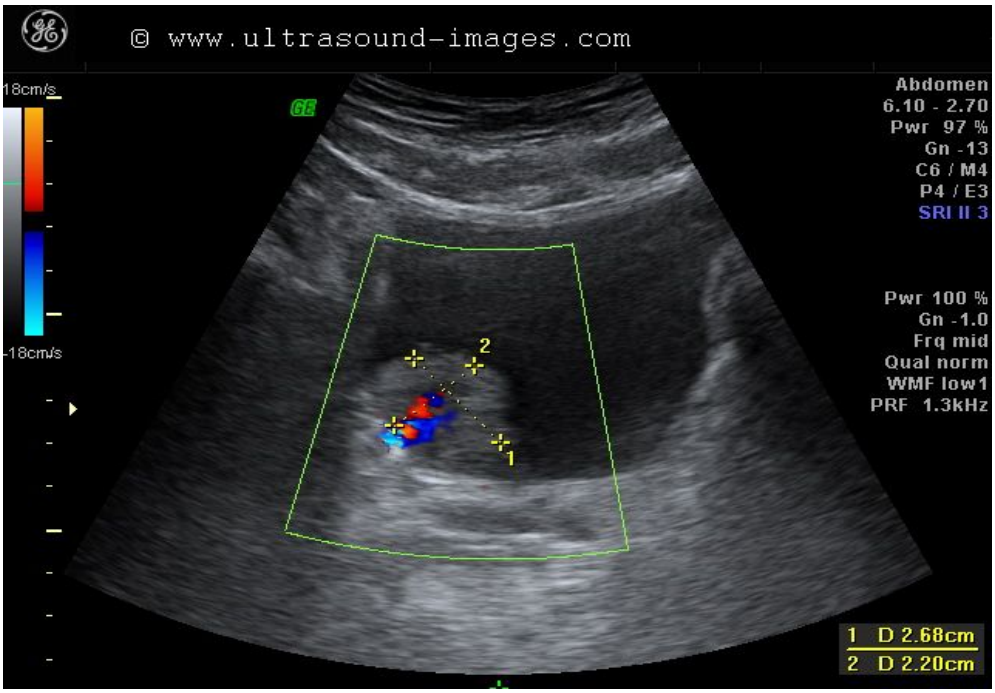
HISTOLOGICAL PICTURE



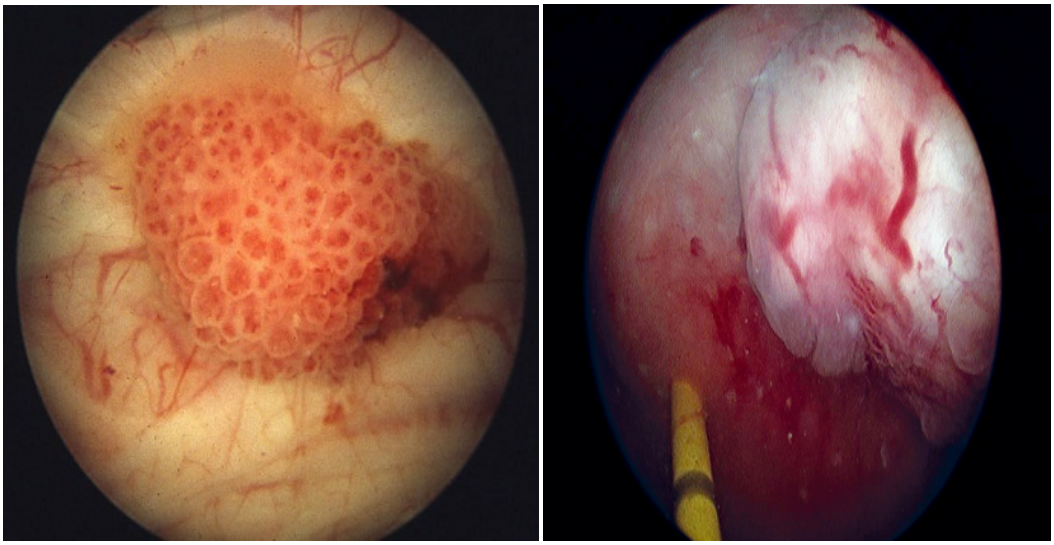
Histology of high grade papillary TCC. H&E (100X).



Histology of TCC with muscle invasion. H&E (400X)



Ultrasound picture shows non muscle invasive tumours over Right lateral wall of bladder (hypoechoic)



Cystoscopy shows non-muscle invasive and muscle invasive tumours

ANALYSIS

In our Prospective clinical study, totally 70 patients were included those who are presented with Lower urinary tract symptoms due to Bladder TCC detected by ultrasound. Age of patient ranged from 40 to 89. Most common age group 50-59 years (49%). Male to Female ratio – 4:1

The main clinical presentations were hematuria, dysuria & increased frequency of micturition . Most patients about 34, presented with features of hematuria, dysuria, & Frequency of micturition. 22 patients presented with hematuria & dysuria, 10 patients with hematuria & frequency of micturition. Only 4 patients presented with dysuria & frequency of micturition.

Out of 70 cases, 74% were smokers, remaining 26% were non-smoker. The smokers were found to be more prone to develop neoplastic lesion in bladder. Urine cytology were positive for cancer cells in 44(63%), suscipious in 8(11%), Atypical in 4(6%), and negative in 14 (20%). For comparative study with histopathological correlation, positive cytology & were suscipious grouped as Positive, Atypical & Negative were grouped as Negative.

Lesions in ultrasound in bladder TCC were mostly hypoechoic of which some were irregular, some lobulated and some pedunculated. Most of lesions are multiple & few are single. Hypoechoic lesion were

followed by mixed echoic, few hyperechoic in decreased order of frequency.

Statisticaly incidence of USG hypoechogenic lesions is 44.44% in Urine Cytology –ve Group compared to 69.23% in Urine Cytology +ve group with a p-value of 0.028 according to Chi-Squared test. This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance

In cystoscopy, lesions were mostly situated in lateral wall in 38 cases, followed by Postero-lateral, base & neck of bladder, dome of bladder and anterior wall respectively. The association between location of Lesions and Urine Cytology Findings is considered to be not statistically significant since $p > 0.05$.

Our study shows Most of lesions are sessile (60%), followed by pedunculated (40%). Multiple tumours are present in 28 cases, single tumours in 48 cases. Likewise, tumour size < 2cm present in 10 cases, 2-5cm seen in 44 cases, > 5cm in 16 patients. Cytopositivity was found to more with single, large & sessile tumours than multiple, small pedunculated tumour. Size of tumour increase with increase in cytopositivity. When tumour size >5cm & above there is about 90-100% cytopositivity was observed. The association between Number & size of Tumours and Urine Cytology Findings is considered to be not statistically significant since $p > 0.05$.

In our study group, among 70 cases, 68 cases were confirmed histologically, of which 24 cases of low grade TCC, 44 cases of High grade TCC, only 2 cases are histologically negative.

Out of 68 cases of histologically proved TCC, 52 cases were correctly diagnosed by urine cytological examination. Only 16 cases have cytological negative, 2 cases cytological negative due to benign disorder like papillary cystitis. Among cytological negative 16 cases, 10 cases were diagnosed as low grade in histopathology

Histological confirmed High grade TCC in 44 patient, of which 36 patient were detected cytological i.e (86%) detected by cytology. Histological confirmed low grade TCC occur in 24 patients of which 16 patients were detected cytologically (58%). Finally histological confirmed TCC occur in 68 patients on which 52 patients were diagnosed cytologically (76%). Statistically the incidence of High Grade Histological Positivity is 50% in Urine Cytology –ve Group compared to 69.23% in Urine Cytology +ve group with a p-value of 0.033 according to Chi-Squared test. This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance. Statistically P value-0.033 is significiant

In our study group, consists of 10 patients of PTa, 21 patients of carcinoma in situ PTis, 14 patients invaded subepithelial connective tissue PT1, 25 patients have muscle invasive PT2 & above. Urine cytology was positive in 4 cases of PTa, 15 cases of Tis, 12 cases of PT1, 21 cases of PT2 & above. In 6 cases of PTa, 6 cases of PTis, 2 cases of PT1, 4 cases of PT2 & above staging were found to have urine cytology negative. About 80% of noninvasive Tumour had negative urine cytology. Statisticially the incidence of PT 2 and above Tumour Staging is 22.22% in Urine Cytology –ve Group compared to 40.38% in Urine Cytology +ve groupwith a p-value of 0.038 according to Chi-Squared test. This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance . Cytopositivity increases with increase in Grade & Stage of tumour.

Out of 70 patients histologically , 68 patients had varying grades of Bladder Transitional cell carcinoma, 2 Patients had adenocarcinoma . Incidence of T-cell Carcinoma type is 88.99% in Urine Cytology –ve Group compared to 100% in Urine Cytology +ve group with a p-value of 0.015 according to Chi-Squared test.

DISCUSSION

DISCUSSION

Urine cytology is a non invasive method of detection, diagnosis and follow up of bladder transtitional cell carcinomas. Urine cytology involves exfoliated cells from lining of urinary tract. Specimen collected from voided urine and should be processed immediately or refrigerated as soon as possible. It can be useful investigation for individuals with hematuria, has been own draw backs.

Urine cytology relies on neoplastic cells being shed in urine. High grade tumours like CIS are more likely to shed abnormal cells into urine. Sensitivity rates are higher for high grade tumours. Low grade tumours are less likely to shed cells into urine and less sensitivity. Exfoliated cells are usually shed in clusters rather than single cells. False positive due to stones , infections, instrumentation and chemo/radiotherapy .

Urine cytology reported as suscipous of malignancy require further evaluation. Most of these studies shows that outcome of patients having atypical urine cytology shows that less than 50% of individuals are 30% are found to have malignancy. It requires further follow up, currently large number of patients are subjected to unnecessary investigations with time and resources lost.

Patients were selected on basis of clinical features and ultrasonographic features. Only those cases diagnosed as urinary bladder lesions by USG were included in the study. Out of 70 cases, age of the patients ranged from 40-80 years and most of the patients were in sixth decade of life. The male to female ratio was 4:1.

The most common clinical presentations were hematuria, dysuria and increased frequency of micturition followed by presented with hematuria & dysuria, hematuria and frequency of micturition.

Most of the patients in the study were smokers. Out of 70, smokers were majority in about 74%. So there was strong association between smoking and bladder neoplasms

The lesion in ultrasonography were mostly hypoechoic (42), of which some where irregular, lobulated, pedunculated. Some of the lesions were multiple and few are single. This was followed by mixed echoic masses, hyperechoic and isoechoic lesions. **Its Clinical Significance**, incidence of USG hypoechogenic lesions was meaningfully 24.79 percentage points more in Urine Cytology +ve group compared to Urine Cytology –ve group In our study Urine Cytology Positivity leads to 1.56 times increase in occurrence of USG hypoechogenic lesions

Urine samples are freshly whole voided post ambulatory specimen**,** collected randomly and processed immediately. After detection of growth by USG, cytology as a screening technique.

To detect malignant lesions by cytology depend upon morphological features of atypical cells namely cellularity, clusters, papilla, alteration in cell type, shape, size, comet cells , necrosis, nuclear membrane irregularity, high N:C ratio and nuclear hyperchromasia Urine cytology were positive for cancer cells in 44(63%), suscipious in 8(11%), Atypical in 4(6%), and negative in 14 (20%). For comparative study with histopathological correlation, positive cytology & were suscipious grouped as Positive, Atypical & Negative were grouped as Negative.

The macroscopic appearance of growth in bladder cystoscopy were mainly sessile followed by pedunculated. About 48 cases are single and 28 cases are multiple. Most of lesions were situated in lateral walls, namely right and left lateral walls. The remaining were located in postero lateral, base & neck and dome of bladder. The patients who have lesions in base and neck of bladder presented with increased frequency of micturition.

Likewise, tumour size < 2cm present in 14%, 2-5cm seen in 62%, > 5cm in 22% patients. Cytopositivity was found to more with single , large & sessile tumours than multiple, small pedunculated tumour. Size of tumour

increase with increase in cytopositivity. When tumour size >5cm & above there is about 90-100% cytopositivity was observed .

In our study group, among 70 cases, 97% were confirmed histologically, of 34% which of low grade TCC, 63% of High grade TCC, only 2 cases are histologically negative.

Out of 68 cases of histologically proved TCC, 72% were correctly diagnosed by urine cytological examination. Only 25% cases have cytological negative, 2 cases cytological negative due to benign disorder like papillary cystitis. Among cytological negative ,38% were diagnosed as low grade in histopathology.

Histological confirmed High grade TCC in 44 patient, of which 86% patient were detected cytological . Histological confirmed low grade TCC occur in 24 patients of which 58% patients were detected cytologically. Finally histological confirmed TCC occur in 68 patients on which 76% patients were diagnosed cytologically. It's Clinical Significance the incidence of High Grade Histological Positivity was meaningfully 19.23 percentage points more in Urine Cytology +ve group compared to Urine Cytology –ve group . Urine Cytology Positivity leads to 1.38 times increase in occurrence of High Grade Histological Positivity. Our study conclude that Urine Cytology Positivity can predict an increasing trend of High Grade Histological Positivity

In our study group, Urine cytology was positive in 7% cases of PTa, 28% cases of Tis, 23% cases of PT1, 40% cases of PT2 & above.. About 80% of noninvasive Tumour had negative urine cytology. Its **Clinical Significance** the incidence of PT 2 and above Tumour Staging was meaningfully 18.16 percentage points more in Urine Cytology +ve groupcompared to Urine Cytology –ve group**.** Urine Cytology Positivity leads to 1.82 times increase in occurrence of PT2 and above Tumour Staging. Our **study** conclude that Urine Cytology Positivity is detrimental in nature and can lead to an increasing trend of Higher levels of tumour staging

Out of 70 patients histologically, 68 patients had varying grades of Bladder Transitional cell carcinoma, 2 Patients had adenocarcinoma. Its **Clinical Significance** the incidence T-cell Carcinoma type was meaningfully 11.1 percentage points more in Urine Cytology +ve group compared to Urine Cytology –ve group. Urine Cytology Positivity leads to 1.12 times increase in occurrence of T-cell Carcinoma type. Our study group conclude that Urine Cytology Positivity is detrimental in nature and can lead to an increasing trend of Transtitional cell Carcinoma type

Stromal invasion by urothelial carcinoma proceeds in two stages, invasionof lamina propria and invasion of muscle layer. Muscle invasion found in 25 cases

Urothelial bladder malignancies diagnosed by combination of cystoscopy and biopsy, with cytology as a screening procedure. Accuracy of cytological diagnosis depend upon experience and vary from cone cytologist to another. Cytological findings alone cannot be diagnostic in many cases, they require clinical and radiological findings also.

Urine cytology is used for diagnosis of clinical symptomatic patients, detection of tumours in high risk patients those who exposure to industrial chemicals, smoking. Cytology only complements, does not replace cystoscopy and biopsy. Cytology useful in detection in small or hidden lesions like diverticulum, ureters, renal pelvis, urethra.

Incidence of urothelial carcinoma increases, so demand for urine cytology increases. Clinical history is important to minimise false positive . Urine cytology sensitivity increases with grade of tumour

To conclude that sensitivity of urine cytology was 96% where as specificity was 26% . Sensitivity for high grade tumous was higher than low grade tumours. Its **Diagnostic Significance,** Sensitivity of Urine Cytology study findings is High, meaning that malignancy +ve test result often occurs in those with malignancy. Specificity of Urine Cytology study findings is extremely low, meaning that malignancy –ve test very rarely occurs in those without malignancy.

The PPV of Urine Cytology study findings are modest, meaning false positives are little common in those who screen positive. The NPV of Urine Cytology study findings is very high, meaning false negatives are rare in those who screen negative.

LH ratio for positive test is high, meaning that the test is more indicative of malignancy. It is good in ruling-in malignancy .LH ratio for negative test is not very low, meaning that it is more likely the negative test result is to occur in a patient than in a subject without disease. It is not good in ruling-out malignancy

The diagnostic effectiveness or diagnostic accuracy is very high. It means that the overall value of Urine Cytology study in detecting malignancy as a combined screening and case-finding test is good. Prevalence of this condition is very common. Our study shows that cyto - histological correlation was 76%.

Although specificity for urine cytology is low, its high sensitivity shows still a valuable tool in diagnosis of bladder carcinoma, where newer modalities have not yet been established. Larger studies may be required to better study specificity and sensitivity of urine cytology.

CONCLUSION

CONCLUSION

- Cytological examination of urine specimen is valuable as an aid in the diagnosis of bladder tumors.
- Voided urine cytology correlates with histological diagnosis in more than 60% of cases.
- Accuracy is more with high grade tumors
- Urine cytology grading correlates in most cases with histopathological grading.
- The voided urine cytology is not only of diagnostic, but also of prognostic value; positive cytology of high grade presumably identifies patients at high risk for high grade and invasive tumours.
- Cystoscopy is essential in diagnosing low grade tumors which were mostly missed by voided urine cytology.
- Voided urine cytological study can be a valuable adjunct to the clinician in the evaluation of suspected urothelial malignancy, as it is simple, non-invasive and with good accuracy in the diagnosis of TCC.

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BIBLOGRAPHY

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ANNEXURES

ANNEXURE 1

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.6371/ME-1/Ethics/2014 Dt:04.09.2014.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Prospective Study of comparison of urinay cytology with histopathological examination in bladder transitional cell carcinoma" - For Project Work submitted by Dr.P.Vijayakumar, MCh Urology, PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE * Kilpauk, Chennai-10. * 29 SEP 2014

29/9/14

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

26/9/2014
29/9/14

ANNEXURE - 2

PROFORMA

NAME: AGE: SEX:

ADDRESS: IP.NO:

D.O.A: D.O.S: D.O.D:

PRESENTING COMPLAINTS:

Hematuria Dysuria Frequency of Micturition

GENERAL EXAMINATION: P.R: B.P:

PER ABDOMEN:

INVESTIGATIONS:

HB%: PCV%

BLOOD: UREA- SUGAR

SERUM CREATININE- ELECTROLYTES

URINE C/S:

URINE CYTOLOGY

POSITIVE NEGATIVE SUSPCIOUS ATYPIA

USG KUB:

GROWTH

HYPERECHOIC HYPOECHOIC

MIXED ECHOIC ISOECHOIC

CYSTOSCOPY:

TYPE OF LESION

PEDUNCULATED

SESSILE

LOCATION OF TUMOUR

LATERAL WALL

ANTERIOR WALL

POSTERIOR WALL

BASE & NECK OF BLADDER

NUMBER

SINGLE

MULTIPLE

SIZE OF TUMOUR

<2cm 2-5 cm > 5cm

POST OP BIOPSY:

HISTOLOGY

TRANSITIONAL CELL CARCINOMA

GRADE I pTa

GRADE II pTis

GRADE III pT1

p T2 & above

IMPRESSION:

ANNEXURE 3

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

சிறுநீரக அறுவை சிகிச்சை பிரிவு

கீழ்ப்பாக்கம் மருத்துவக் கல்லூரி

பங்கு பெறுபவரின் பெயர்

பங்கு பெறுபவரின் எண்

பங்கு பெறுபவர் இதனை (√) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன். ☐

நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்தும் கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறோன். ☐

இந்த ஆய்வில் ஒருமுறை 5 மி இரத்தம் பரிசோதனைக்காக எடுத்துக் கொள்ளப்படும் என்பதை அறிவேன். ☐

பங்கேற்பவரின் கையொப்பம்_____இடம் _____

தேதி இடம் _____தேதி_____

பங்கேற்பவரின் பெயர் மற்றும் விலசம்
சாட்சியாளரின் கையொப்பம்

இடம் _____ தேதி _____
சாட்சியாளரின் பெயர் மற்றும் விலாசம்

ஆய்வாளரின் கையொப்பம்
இடம் _____ தேதி _____

ஆய்வாளரின் பெயர் _____

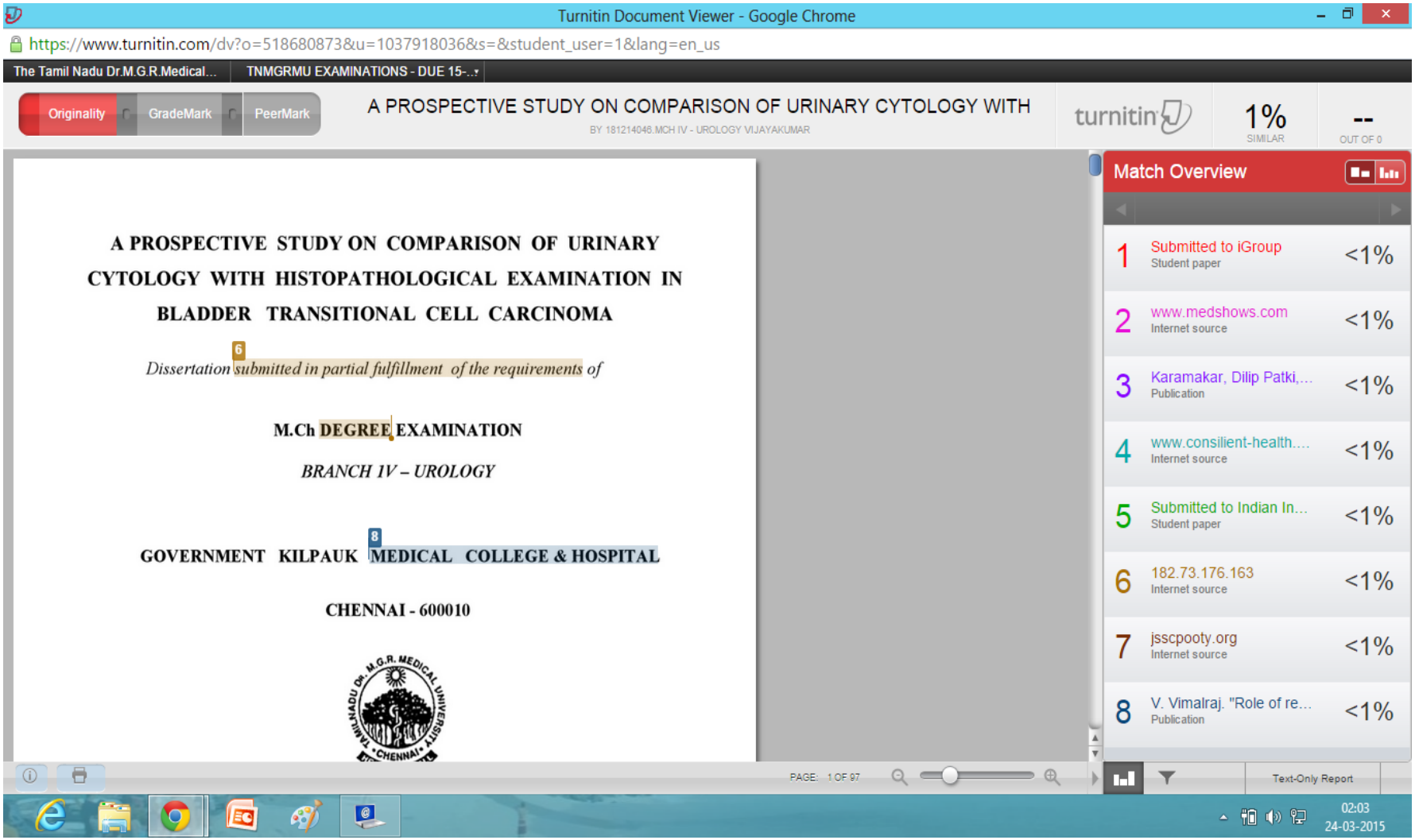
MASTER CHART

MASTER CHART

S. NO	Name	Age/Sex	IP NO	Clinical Features	Smoking	Urine cytology				Ultrasound findings	Location of lesions	Type of lesions	No of tumours	Tumour Size	Histological diagnosis			Tumour staging	Type of Tumour
						Positive	*Suspicious*	*Atypical*	*Negative*						*Low grade*	*High grade*	*Negative*		
1	Gunalan	62/M	2197	HDF	P	*				HYPO	LAT	SES	S	2=5		*		PT2	TCC
2	Krishnamoorthy	51/M	3435	HD	P	*				MIXED	POST	SES	S	2=5		*		PT1	TCC
3	Malliga	52/F	3428	HF		*				HYPO	LAT	PED	M	>5	*			PTis	TCC
4	Ganesan	67/M	3455	HDF	P	*				HYPO	BASE	SES	M	2=5		*		PT2	TCC
5	Janaki	63/F	1432	HDF					*	HYPO	LAT	SES	S	2=5	*			PT1	TCC
6	Nelson	52/M	1899	HD	P	*				MIXED	POST	PED	S	<2	*			PT2	TCC
7	Vasudevan	54/M	14377	HDF	P	*				HYPO	DOME	SES	M	>5		*		PT2	TCC
8	Ravi	66/M	14223	HDF				*		HYPER	POST	PED	S	2=5	*			PTis	TCC
9	Sundaran	55/M	42292	HD	P	*				HYPO	LAT	SES	M	2=5		*		PTis	TCC
10	Sudharasan	72/M	1419	HDF	P	*				HYPO	BASE	SES	S	2=5	*			PT1	TCC
11	Kathiresan	64/M	11986	DF	P		*			MIXED	LAT	PED	M	<2		*		PT2	TCC
12	Dhanaammal	56/F	11288	HD		*				MIXED	LAT	PED	M	2=5		*		Pta	TCC
13	Mahanathan	34/M	11331	HDF	P				*	HYPO	LAT	SES	S	2=5		*		PTa	TCC
14	Samuvel	47/M	114794	HDF	P	*				HYPO	POST	SES	M	2=5		*		PTis	TCC
15	Veeramani	56/M	2372	HDF		*				ISO	LAT	PED	S	2=5		*		PT1	TCC
16	Shanthi	53/F	4099	HF	P				*	MIXED	BASE	PED	M	>5	*			PTa	TCC
17	Kothandaraman	57/M	4093	HD	P	*				HYPO	LAT	SES	M	2=5		*		PT2	TCC
18	Arumugam	69/M	5335	HDF	P	*				HYPO	POST	PED	S	2=5		*		PTis	TCC
19	Sankaramoorthy	56/M	6045	HF	P	*				HYPO	ANT	PED	S	2=5		*		PT2	TCC
20	Ansar basha	59/M	7098	HD			*			HYPER	LAT	PED	M	>5	*			PTis	TCC
21	Ponnusamy	52/M	7089	HF	P				*	HYPO	LAT	PED	M	>5		*		PTa	TCC
22	Shanmugam	77/M	1077	HDF	P	*				MIXED	BASE	SES	S	2=5		*		PT1	TCC
23	Janarthan	66/M	16873	HD	P				*	HYPO	POST	SES	S	2=5			*	PT2	ADENO
24	Murugammal	59/F	20351	HDF	P			*		HYPO	LAT	SES	M	>5	*			PTis	TCC
25	Loganathan	56/M	23546	HF	P	*				MIXED	LAT	PED	M	2=5		*		PT2	TCC
26	Vignesh	48/M	2181	HDF	P	*				HYPO	LAT	PED	S	2=5	*			PTis	TCC
27	Soundappan	49/M	23782	HDF		*				HYPO	LAT	SES	M	2=5	*			PT2	TCC
28	Babu	67/M	2376	DF	P	*				HYPO	POST	SES	S	2=5	*			PT2	TCC
29	Parthasarthy	51/M	8754	HD	P	*				HYPO	LAT	PED	S	<2		*		PT1	TCC
30	Leelavathy	51/F	5277	HDF	P		*			HYPER	BASE	SES	S	>5		*		PTis	TCC
31	Suresh	56/M	2341	HD					*	MIXED	LAT	SES	S	2=5		*		PT1	TCC
32	Narasiman	59/M	5273	HDF	P	*				HYPO	POST	SES	M	2=5	*			PTis	TCC
33	Sivasamy	68/M	5460	HDF	P	*				HYPO	LAT	PED	S	2=5	*			PT2	TCC
34	Srinivasan	47/M	2587	HD	P				*	HYPO	LAT	PED	M	2=5		*		PTa	TCC
35	Chanadrasekar	52/M	3098	HF		*				ISO	LAT	SES	S	>5	*			PT2	TCC
36	Selvi	56/F	5469	HDF		*				MIXED	LAT	PED	S	2=5		*		PT1	TCC

37	Ruban	54/M	7045	HDF	P	*				HYPO	LAT	SES	M	<2	*			PTis	TCC
38	SUBRAMANI	69/M	2114	DF	P	*				HYPO	POST	SES	S	2=5		*		PT2	TCC
39	Selvamani	38/M	1232	HDF	P		*			MIXED	LAT	SES	M	2=5		*		PTis	TCC
40	Balakrishnan	73/M	1410	HD	P				*	HYPO	LAT	SES	S	>5	*			PTa	TCC
41	Dhanasingh	55/M	1178	HDF	P	*				HYPER	POST	SES	M	2=5		*		PT2	TCC
42	Ameen	59/M	7155	HDF	P	*				HYPO	BASE	PED	S	2=5	*			PT1	TCC
43	Ganesan	45/M	3099	HD	P	*				HYPO	LAT	PED	S	2=5		*		PTis	TCC
44	Raju	62/M	3128	HF	P	*				HYPO	LAT	SES	S	>5		*		PT2	TCC
45	Kaliammal	64/F	3944	HDF			*			MIXED	POST	PED	M	2=5		*		PT2	TCC
46	Chelladurai	58/M	4062	HDF	P	*				HYPO	LAT	SES	S	<2		*		PTis	TCC
47	Selvamani	66/M	4064	HD	P			*		MIXED	DOME	SES	S	2=5	*			PTa	TCC
48	Narayanan	54/M	4068	HDF					*	HYPO	LAT	PED	S	<2		*		PTis	TCC
49	Ethir	72/M	4095	HD	P	*				HYPO	BASE	SES	M	>5		*		PTis	TCC
50	Chelladurai	44/M	7389	HD	P				*	HYPER	LAT	PED	S	2=5			*	PT2	ADENO
51	Velusamy	67/M	7450	HDF			*			MIXED	LAT	PED	S	2=5	*			PT1	TCC
52	Arumugam	53/M	7653	HD	P	*				HYPO	POST	SES	S	2=5		*		PTa	TCC
53	Narasiman	71/M	7822	HD	P	*				HYPO	LAT	SES	M	<2		*		PT2	TCC
54	Sivasamy	42/M	7709	HDF	P	*				ISO	LAT	PED	S	>5	*			PTis	TCC
55	Porkaipandian	69/M	11986	HD		*				HYPO	ANT	SES	S	<2		*		PT1	TCC
56	Singaravel	56/M	11288	HD	P	*				MIXED	POST	SESS	M	2=5	*			PT2	TCC
57	Tamil selvi	67/F	11331	HDF	P		*			HYPO	BASE	SES	S	2=5		*		PT2	TCC
58	Chanadran	82/M	11479	DF	P				*	HYPO	LAT	SES	S	2=5		*		PTa	TCC
59	Vajram	58/M	12374	HD		*				HYPO	DOME	SES	M	2=5		*		PT1	TCC
60	Selvamani	61/M	14909	HDF		*				ISO	POST	PED	S	>5		*		PTis	TCC
61	Karthika	42/F	15335	HF	P				*	HYPO	BASE	SES	S	2=5		*		PT2	TCC
62	Perumal	59/M	15083	HDF	P			*		HYPO	LAT	SES	M	>5		*		PT1	TCC
63	Kannan	63/M	17098	HD	P		*			MIXED	LAT	SES	S	2=5		*		PT2	TCC
64	Karupiah	44/M	16788	HDF	P				*	HYPO	POST	SES	S	2=5	*			PTa	TCC
65	Madhu	57/F	22783	HD	P	*				HYPER	LAT	SES	M	>5		*		PT2	TCC
66	Rangasamy	69/M	22782	HDF	P	*				HYPO	BASE	PED	S	2=5		*		PTis	TCC
67	Veeran	54/M	20365	HDF	P	*				HYPO	ANT	SES	M	<2		*		PT1	TCC
68	Meeran	42/M	22782	HD		*				MIXED	POST	SES	M	2=5	*			PTis	TCC
69	Govindasamy	55/M	76542	HDF	P	*				HYPO	LAT	SES	S	>5		*		PT2	TCC
70	Geetha	45/F	45677	HDF	P				*	HYPO	LAT	SES	S	2=5		*		PTis	TCC

ANNEXURE -4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